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TITLE

Alpha-Ketoamide Inhibitors of Hepatitis C Virus NS3
Protease

FIELD OF THE INVENTION

10 The present invention relates generally to a novel class of alpha-ketoamides which are useful as serine protease inhibitors, and more particularly as Hepatitis C virus NS3 protease inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds and methods of using the same.

BACKGROUND OF THE INVENTION

15

Hepatitis C virus (HCV) is the major cause of transfusion and community-acquired non-A, non-B hepatitis worldwide. Approximately 2% of the world's population are infected with the virus. In the United States, hepatitis C
20 represents approximately 20% of cases of acute hepatitis. Unfortunately, self-limited hepatitis is not the most common course of acute HCV infection. In the majority of patients, symptoms of acute hepatitis resolve, but alanine aminotransferase (a liver enzyme diagnostic for liver
25 damage) levels often remain elevated and HCV RNA persists. Indeed, a propensity to chronicity is the most distinguishing characteristic of hepatitis C, occurring in at least 85% of patients with acute HCV infection. The factors that lead to chronicity in hepatitis C are not well
30 defined. Chronic HCV infection is associated with increased incidence of liver cirrhosis and liver cancer. No vaccines are available for this virus, and current treatment is restricted to the use of alpha interferon, which is effective in only 15-20% of patients. Recent
35 clinical studies have shown that combination therapy of alpha interferon and ribavirin leads to sustained efficacy in 40% of patients (Poynard, T. et al. *Lancet* **1998**, 352, 1426-1432.). However, a majority of patients still either fail to respond or relapse after completion of therapy.

5 Thus, there is a clear need to develop more effective
therapeutics for treatment of HCV-associated hepatitis.

HCV is a positive-stranded RNA virus. Based on
comparison of deduced amino acid sequence and the extensive
similarity in the 5' untranslated region, HCV has been
10 classified as a separate genus in the Flaviviridae family,
which also includes flaviviruses such as yellow fever virus
and animal pestiviruses like bovine viral diarrhea virus
and swine fever virus. All members of the Flaviviridae
15 stranded RNA genome encoding all known virus-specific
proteins via translation of a single, uninterrupted, open
reading frame.

Considerable heterogeneity is found within the
nucleotide and encoded amino acid sequence throughout the
20 HCV genome. At least six major genotypes have been
characterized, and more than 50 subtypes have been
described. The major genotypes of HCV differ in their
distribution worldwide, and the clinical significance of
the genetic heterogeneity of HCV remains elusive despite
25 numerous studies of the possible effect of genotypes on
pathogenesis and therapy.

The RNA genome is about 9.6 Kb in length, and encodes
a single polypeptide of about 3000 amino acids. The 5'
untranslated region contains an internal ribosome entry
30 site (IRES), which directs cellular ribosomes to the
correct AUG for initiation of translation. As was
determined by transient expression of cloned HCV cDNAs, the
precursor protein is cotranslationally and
posttranslationally processed into at least 10 viral
35 structural and nonstructural (NS) proteins by the action of
a host signal peptidase and by two distinct viral
proteinase activities. The translated product contains the
following proteins: core-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-
NS5B.

40 The N-terminal portion of NS3 functions as a
proteolytic enzyme that is responsible for the cleavage of
sites liberating the nonstructural proteins NS4A, NS4B,

5 NS5A, and NS5B. NS3 has further been shown to be a serine
protease. Although the functions of the NS proteins are
not completely defined, it is known that NS4A is a protease
cofactor and NS5B is an RNA polymerase involved in viral
10 processing of the viral polyprotein are expected to have
antiviral activity.

There are several patents which disclose HCV NS3
protease inhibitors. WO98/17679 describes peptide and
peptidomimetic inhibitors with the following formula: U-E⁸-
15 E⁷-E⁶-E⁵-E⁴-NH-CH(CH₂G¹)-W¹, where W is one of a variety of
electrophilic groups, including boronic acid or ester. E⁴
represents either an amino acid or one of a series of
peptidomimetic groups, the synthesis of which are not
exemplified. HCV protease inhibitors described in the
20 present case are not covered.

Based on the large number of persons currently
infected with HCV and the limited treatments available, it
is desirable to discover new inhibitors of HCV NS3
protease.

25

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to
provide novel HCV NS3 protease inhibitors.

It is another object of the present invention to
30 provide a novel method of treating HCV infection which
comprises administering to a host in need of such treatment
a therapeutically effective amount of at least one of the
compounds of the present invention or a pharmaceutically
acceptable salt form thereof.

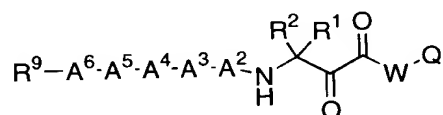
35 It is another object of the present invention to
provide pharmaceutical compositions with HCV NS3 protease
inhibiting activity comprising a pharmaceutically
acceptable carrier and a therapeutically effective amount
of at least one of the compounds of the present invention
40 or a pharmaceutically acceptable salt form thereof.

5 It is another object of the present invention to provide a method of inhibiting HCV present in a body fluid sample which comprises treating the body fluid sample with an effective amount of a compound of the present invention. It is another object of the present invention to provide a
10 kit or container containing at least one of the compounds of the present invention in an amount effective for use as a standard or reagent in a test or assay for determining the ability of a potential pharmaceutical to inhibit HCV NS3 protease, HCV growth, or both.

15 It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of HCV.

20 These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of Formula (I):



(I)

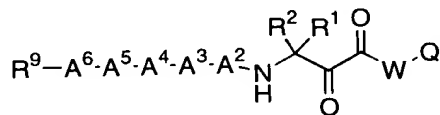
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wherein W, Q, R¹, R², A², A³, A⁴, A⁵, A⁶, and R⁹, are defined below, stereoisomeric forms, mixtures of stereoisomeric forms, or pharmaceutically acceptable salt
30 forms thereof, are effective HCV NS3 protease inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides a novel compound of Formula I:

35



(I)

5

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

W is -NH- or -O-;

10

Q is selected from: $-(CR^{10}R^{10c})_n-Q^1$, $-(CR^{10}R^{10c})_n-Q^2$,

C₁-C₄ alkyl substituted with Q¹,

C₂-C₄ alkenyl substituted with Q¹,

C₂-C₄ alkynyl substituted with Q¹, and

15

an amino acid residue;

Q¹ is selected from:

-CO₂R¹¹, -SO₂R¹¹, -SO₃R¹¹, -P(O)₂R¹¹, -P(O)₃R¹¹,

aryl substituted with 0-4 Q^{1a}, and

20

5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, said heterocyclic group substituted with 0-4 Q^{1a};

25 Q^{1a} is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃, -CH₃,

-OCH₃, -CO₂R¹⁹, -C(=O)NR¹⁹R¹⁹, -NHC(=O)R¹⁹, -SO₂R¹⁹,

-SO₂NR¹⁹R¹⁹, -NR¹⁹R¹⁹, -OR¹⁹, -SR¹⁹, C₁-C₄ alkyl,

C₁-C₄ alkoxy, C₁-C₄ haloalkyl, or C₁-C₄ haloalkoxy;

30 R¹⁹ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, aryl, aryl(C₁-C₄ alkyl), C₃-C₆ cycloalkyl, or C₃-C₆ cycloalkyl(C₁-C₄ alkyl);

35 alternatively, NR¹⁹R¹⁹ may form a 5-6 membered heterocyclic group consisting of carbon atoms, a nitrogen atom, and optionally a second heteroatom selected from the group: O, S, and N;

40 R¹⁰ is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, and C₁-C₆ alkyl substituted with 0-1 R^{10a};

5

R^{10a} is selected from the group: halo, -NO₂, -CN, -CF₃,
-CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹, -SR¹¹, -C(=NH)NH₂, and aryl
substituted with 0-1 R^{10b};

10 R^{10b} is selected from the group: -CO₂H, -NH₂, -OH, -SH, and
-C(=NH)NH₂;

R^{10c} is H or C₁-C₄ alkyl;

15 alternatively, R¹⁰ and R^{10c} can be combined to form a C₃-C₆
cycloalkyl group substituted with 0-1 R^{10a};

R¹¹ is, at each occurrence, independently H or C₁-C₄ alkyl;

20 R^{11a} is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₄ alkenyl,
C₂-C₄ alkynyl, aryl, aryl(C₁-C₄ alkyl)-,
C₃-C₆ cycloalkyl, or C₃-C₆ cycloalkyl(C₁-C₄ alkyl)-;

Q² is -X-NR¹²-Z, -NR¹²-Y-Z, or -X-NR¹²-Y-Z;

25

X is selected from the group: -C(=O)-, -S-, -S(=O)-,
-S(=O)₂-, -P(O)-, -P(O)₂-, and -P(O)₃-;

30 Y is selected from the group: -C(=O)-, -S-, -S(=O)-,
-S(=O)₂-, -P(O)-, -P(O)₂-, and -P(O)₃-;

R¹² is H or C₁-C₄ alkyl;

35 Z is C₁-C₄ haloalkyl,
C₁-C₄ alkyl substituted with 0-3 Z^a,
C₂-C₄ alkenyl substituted with 0-3 Z^a,
C₂-C₄ alkynyl substituted with 0-3 Z^a,
C₃-C₁₀ cycloalkyl substituted with 0-5 Z^b,
C₃-C₁₀ carbocycle substituted with 0-5 Z^b,

5 aryl substituted with 0-5 Z^b,
5-10 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, said heterocyclic group substituted
with 0-4 Z^b;
10 an amino acid residue, or
-A⁷-A⁸-A⁹;

Z^a is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
-CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
15 -NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,
C₁-C₄ haloalkoxy,

C₃-C₁₀ cycloalkyl substituted with 0-5 Z^b,
20 C₃-C₁₀ carbocycle substituted with 0-5 Z^b,
aryl substituted with 0-5 Z^b, or
5-10 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, said heterocyclic group substituted
25 with 0-4 Z^b;

Z^b is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
-CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
-NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
30 C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,
C₁-C₄ haloalkoxy,

C₃-C₁₀ cycloalkyl substituted with 0-5 Z^c,
C₃-C₁₀ carbocycle substituted with 0-5 Z^c,
35 aryl substituted with 0-5 Z^c, or
5-10 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, said heterocyclic group substituted
with 0-4 Z^c;

5

Z^c is H, F, Cl, Br, I, $-NO_2$, $-CN$, $-NCS$, $-CF_3$, $-OCF_3$,
 $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$,
 $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$,
 C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4
haloalkoxy;

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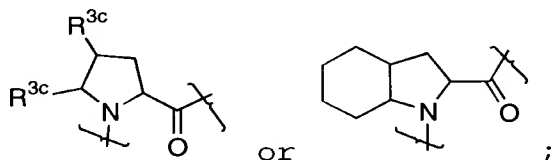
R^{20} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl,
aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or
 C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

15

alternatively, $NR^{20}R^{20}$ may form a 5-6 membered heterocyclic
group consisting of carbon atoms, a nitrogen atom, and
optionally a second heteroatom selected from the
group: O, S, and N;

20

A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, an amino acid residue,



A^3 is a bond, $-NH-CR^5R^6-C(=O)-$, or an amino acid residue;

25

A^4 is a bond, $-NH-CR^7R^8-C(=O)-$, or an amino acid residue;

A^5 is a bond or an amino acid residue;

30

A^7 is a bond or an amino acid residue;

A^8 is an amino acid residue;

35

A^9 is an amino acid residue;

5 R¹ is selected from the group: H, F,
C₁-C₆ alkyl substituted with 0-3 R^{1a},
C₂-C₆ alkenyl substituted with 0-3 R^{1a},
C₂-C₆ alkynyl substituted with 0-3 R^{1a},
aryl substituted with 0-5 R^{1a}, and
10 C₃-C₆ cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:
Cl, F, Br, I, CF₃, CHF₂, OH, =O, SH, -CO₂R^{1b}, -SO₂R^{1b},
-SO₃R^{1b}, -P(O)₂R^{1b}, -P(O)₃R^{1b}, -C(=O)NHR^{1b}, -NHC(=O)R^{1b},
15 -SO₂NHR^{1b}, -OR^{1b}, -SR^{1b}, C₁-C₃ alkyl, C₃-C₆ cycloalkyl,
C₁-C₆ alkoxy, -S-(C₁-C₆ alkyl),
aryl substituted with 0-5 R^{1c},
-O-(CH₂)_q-aryl substituted with 0-5 R^{1c},
-S-(CH₂)_q-aryl substituted with 0-5 R^{1c}, and
20 5-10 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, and substituted with 0-3 R^{1c};

R^{1b} is H,
25 C₁-C₄ alkyl substituted with 0-3 R^{1c},
C₂-C₄ alkenyl substituted with 0-3 R^{1c},
C₂-C₄ alkynyl substituted with 0-3 R^{1c},
C₃-C₆ cycloalkyl substituted with 0-5 R^{1c},
C₃-C₆ carbocycle substituted with 0-5 R^{1c},
30 aryl substituted with 0-5 R^{1c}, or
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, said heterocyclic group substituted
with 0-4 R^{1c};

35 R^{1c} is selected at each occurrence from: C₁-C₄ alkyl, Cl,
F, Br, I, OH, C₁-C₄ alkoxy, -CN, -NO₂, C(O)OR^{1d},
NR^{1d}R^{1d}, CF₃, and OCF₃;

5

R^{1d} is H or C₁-C₄ alkyl;

R² is H, F, or C₁-C₄ alkyl;

10 R³ is selected from the group: H,

C₁-C₆ alkyl substituted with 0-4 R^{3a},

C₂-C₆ alkenyl substituted with 0-4 R^{3a},

C₂-C₆ alkynyl substituted with 0-4 R^{3a},

-(CH₂)_q- C₃-C₆ cycloalkyl substituted with 0-4 R^{3b},

15 -(CH₂)_q-aryl substituted with 0-5 R^{3b}, or

-(CH₂)_q-5-10 membered heterocyclic group consisting of
carbon atoms and 1-4 heteroatoms selected from
the group: O, S, and N, and said heterocyclic
group is substituted with 0-2 R^{3b};

20

R^{3a} is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹,
-SR¹¹, -C(=NH)NH₂, and aryl substituted with R^{10b};

R^{3b} is selected from the group: -CO₂H, - NH₂, -OH, -SH, and
25 -C(=NH)NH₂;

R^{3c} is, at each occurrence, independently selected from: H,
C₁-C₆ alkyl, -OH, and OR^{3d};

30 R^{3d} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,

-(CH₂)_q- C₃-C₆ cycloalkyl, -(CH₂)_q-aryl, or

-(CH₂)_q-(5-10 membered heterocyclic group), wherein
said heterocyclic group consists of carbon atoms
and 1-4 heteroatoms selected from the group: O,
35 S, and N;

R⁴ is selected from the group: H, C₁-C₆ alkyl, phenyl,
phenylmethyl-, phenylethyl-, C₃-C₆ cycloalkyl,
C₃-C₆ cycloalkylmethyl-, and C₃-C₆ cycloalkylethyl-;

5

R⁵ and R⁷ are independently H or R³;

R⁶ and R⁸ are independently H or R⁴;

- 10 R⁹ is selected from the group: -S(=O)R^{9a}, -S(=O)₂R^{9a},
-C(=O)R^{9a}, -C(=O)OR^{9a}, -C(=O)NHR^{9a}, C₁-C₃ alkyl-R^{9a},
C₂-C₆ alkenyl-R^{9a}, and C₂-C₆ alkynyl-R^{9a};

R^{9a} is selected from the group:

- 15 C₁-C₆ alkyl substituted with 0-3 R^{9b},
C₃-C₆ cycloalkyl substituted with 0-3 R^{9c},
aryl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the
20 group: O, S, and N, and said heterocyclic group
is substituted with 0-3 R^{9c};

R^{9b} is selected from the group: phenyl, naphthyl, benzyl,
and 5-10 membered heterocyclic group consisting of
25 carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and R^{9b} is substituted with 0-3
R^{9c};

R^{9c} is selected at each occurrence from the group:

- 30 CF₃, OCF₃, Cl, F, Br, I, =O, OH, phenyl, C(O)OR¹¹, NH₂,
NH(CH₃), N(CH₃)₂, -CN, NO₂;
C₁-C₄ alkyl substituted with 0-3 R^{9d},
C₁-C₄ alkoxy substituted with 0-3 R^{9d},
C₃-C₆ cycloalkyl substituted with 0-3 R^{9d},
35 aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and said heterocyclic group
is substituted with 0-4 R^{9d};

5

R^{9d} is selected at each occurrence from the group:

C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3 , OCF_3 , Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2 , $NH(CH_3)$, $N(CH_3)_2$, -CN, and NO_2 ;

10

an amino acid residue, at each occurrence, independently comprises a natural amino acid, a modified amino acid or an unnatural amino acid wherein said natural, modified or unnatural amino acid is of either D or L configuration;

15

n is 1, 2, 3, or 4; and

p is 1 or 2; and

20

q , at each occurrence, is independently 0, 1 or 2.

[2] In a preferred embodiment, the present invention provides novel compounds of Formula I, wherein:

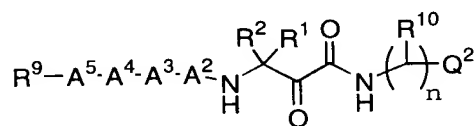
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Q is $-(CR^{10}R^{10c})_n-Q^2$ or

an amino acid residue, wherein the amino acid residue comprises a natural, a modified or an unnatural amino acid.

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[3] In a more preferred embodiment, the present invention provides novel compounds of Formula II, wherein:



(II)

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or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

5 R^{10} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, and C_1-C_6 alkyl substituted with 0-1 R^{10a} ;

R^{10a} is selected from the group: halo, $-NO_2$, $-CN$, $-CF_3$,
10 $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with 0-1 R^{10b} ;

R^{10b} is selected from the group: $-CO_2H$, $-NH_2$, $-OH$, $-SH$, and
 $-C(=NH)NH_2$;

15 R^{10c} is H or C_1-C_4 alkyl;

alternatively, R^{10} and R^{10c} can be combined to form a C_3-C_6 cycloalkyl group substituted with 0-1 R^{10a} ;

20 R^{11} is, at each occurrence, independently H or C_1-C_4 alkyl;

R^{11a} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl,
 C_2-C_4 alkynyl, aryl, aryl(C_1-C_4 alkyl)-,
 C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

25 Q^2 is $-X-NR^{12}-Z$, $-NR^{12}-Y-Z$, or $-X-NR^{12}-Y-Z$;

X is selected from the group: $-C(=O)-$, $-S-$, $-S(=O)-$,
 $-S(=O)_2-$, $-P(O)-$, $-P(O)_2-$, and $-P(O)_3-$;

30 Y is selected from the group: $-C(=O)-$, $-S-$, $-S(=O)-$,
 $-S(=O)_2-$, $-P(O)-$, $-P(O)_2-$, and $-P(O)_3-$;

R^{12} is H or C_1-C_4 alkyl;

35 Z is C_1-C_4 haloalkyl,
 C_1-C_4 alkyl substituted with 0-3 Z^a ,
 C_2-C_4 alkenyl substituted with 0-3 Z^a ,
 C_2-C_4 alkynyl substituted with 0-3 Z^a ,

- 5 C₃-C₁₀ cycloalkyl substituted with 0-5 Z^b,
 C₃-C₁₀ carbocycle substituted with 0-5 Z^b,
 aryl substituted with 0-5 Z^b,
 5-10 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:
 10 O, S, and N, said heterocyclic group substituted
 with 0-4 Z^b;
 an amino acid residue, or
 -A⁷-A⁸-A⁹;
- 15 Z^a is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
 -CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
 -NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
 C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,
 C₁-C₄ haloalkoxy,
- 20 C₃-C₁₀ cycloalkyl substituted with 0-5 Z^b,
 C₃-C₁₀ carbocycle substituted with 0-5 Z^b,
 aryl substituted with 0-5 Z^b, or
 5-10 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:
 25 O, S, and N, said heterocyclic group substituted
 with 0-4 Z^b;
- Z^b is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
 30 -CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
 -NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
 C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,
 C₁-C₄ haloalkoxy,
- 35 C₃-C₁₀ cycloalkyl substituted with 0-5 Z^c,
 C₃-C₁₀ carbocycle substituted with 0-5 Z^c,
 aryl substituted with 0-5 Z^c, or
 5-10 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:

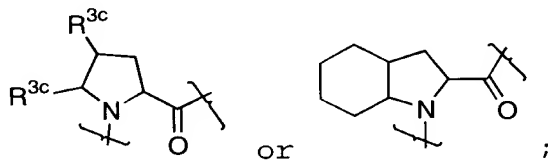
5 O, S, and N, said heterocyclic group substituted
with 0-4 Z^c;

Z^c is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
-CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
10 -NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, or C₁-C₄
haloalkoxy;

R²⁰ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, aryl,
15 aryl(C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl, or
C₃-C₆ cycloalkyl(C₁-C₄ alkyl)-;

alternatively, NR²⁰R²⁰ may form a 5-6 membered heterocyclic
group consisting of carbon atoms, a nitrogen atom, and
20 optionally a second heteroatom selected from the
group: O, S, and N;

A² is a bond, -NH-CR³R⁴-C(=O)-, an amino acid residue,



25 A³ is a bond, -NH-CR⁵R⁶-C(=O)-, or an amino acid residue;

A⁴ is a bond, -NH-CR⁷R⁸-C(=O)-, or an amino acid residue;

30 A⁵ is a bond or an amino acid residue;

A⁷ is a bond or an amino acid residue;

A⁸ is an amino acid residue;

35 A⁹ is an amino acid residue;

5 R^{1a} is selected from the group: H, F,
C₁-C₆ alkyl substituted with 0-3 R^{1a},
C₂-C₆ alkenyl substituted with 0-3 R^{1a},
C₂-C₆ alkynyl substituted with 0-3 R^{1a}, and
C₃-C₆ cycloalkyl substituted with 0-3 R^{1a};

10

R^{1a} is selected at each occurrence from the group:

Cl, F, Br, I, CF₃, CHF₂, OH, =O, SH, -CO₂R^{1b}, -SO₂R^{1b},
-SO₃R^{1b}, -P(O)₂R^{1b}, -P(O)₃R^{1b}, -C(=O)NHR^{1b}, -NHC(=O)R^{1b},
-SO₂NHR^{1b}, -OR^{1b}, -SR^{1b}, C₁-C₃ alkyl, C₃-C₆ cycloalkyl,
15 C₁-C₆ alkoxy, -S-(C₁-C₆ alkyl),
aryl substituted with 0-5 R^{1c},
-O-(CH₂)_q-aryl substituted with 0-5 R^{1c},
-S-(CH₂)_q-aryl substituted with 0-5 R^{1c}, and
5-10 membered heterocyclic group consisting of carbon
20 atoms and 1-4 heteroatoms selected from the group:
O, S, and N, and substituted with 0-3 R^{1c};

R^{1b} is H,

C₁-C₄ alkyl substituted with 0-3 R^{1c},
25 C₂-C₄ alkenyl substituted with 0-3 R^{1c},
C₂-C₄ alkynyl substituted with 0-3 R^{1c},
C₃-C₆ cycloalkyl substituted with 0-5 R^{1c},
C₃-C₆ carbocycle substituted with 0-5 R^{1c},
aryl substituted with 0-5 R^{1c}, or
30 5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, said heterocyclic group substituted
with 0-4 R^{1c};

35 R^{1c} is selected at each occurrence from: C₁-C₄ alkyl, Cl,
F, Br, I, OH, C₁-C₄ alkoxy, -CN, -NO₂, C(O)OR^{1d},
NR^{1d}R^{1d}, CF₃, and OCF₃;

5 R^{1d} is H or C_1 - C_4 alkyl;

R^2 is H, F, or C_1 - C_4 alkyl;

R^3 is selected from the group: H,

- 10 C_1 - C_6 alkyl substituted with 0-4 R^{3a} ,
 C_2 - C_6 alkenyl substituted with 0-4 R^{3a} ,
 C_2 - C_6 alkynyl substituted with 0-4 R^{3a} ,
-(CH_2)_q- C_3 - C_6 cycloalkyl substituted with 0-4 R^{3b} ,
-(CH_2)_q-aryl substituted with 0-5 R^{3b} , and
15 -(CH_2)_q-5-10 membered heterocyclic group consisting of
carbon atoms and 1-4 heteroatoms selected from
the group: O, S, and N, and said heterocyclic
group is substituted with 0-2 R^{3b} ;

- 20 R^{3a} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$,
 $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with R^{10b} ;

R^{3b} is selected from the group: $-CO_2H$, $-NH_2$, $-OH$, $-SH$, and
 $-C(=NH)NH_2$;

- 25 R^{3c} is, at each occurrence, independently selected from: H,
 C_1 - C_6 alkyl, $-OH$, and OR^{3d} ;

- R^{3d} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl,
30 -(CH_2)_q- C_3 - C_6 cycloalkyl, -(CH_2)_q-aryl, or
-(CH_2)_q-(5-10 membered heterocyclic group), wherein
said heterocyclic group consists of carbon atoms
and 1-4 heteroatoms selected from the group: O,
S, and N;

- 35 R^4 is selected from the group: H, C_1 - C_6 alkyl, phenyl,
phenylmethyl-, phenylethyl-, C_3 - C_6 cycloalkyl,
 C_3 - C_6 cycloalkylmethyl-, and C_3 - C_6 cycloalkylethyl-;

5 R⁵ and R⁷ are independently H or R³;

R⁶ and R⁸ are independently H or R⁴;

R⁹ is selected from the group: -S(=O)R^{9a}, -S(=O)₂R^{9a},
10 -C(=O)R^{9a}, -C(=O)OR^{9a}, -C(=O)NHR^{9a}, C₁-C₃ alkyl-R^{9a},
C₂-C₆ alkenyl-R^{9a}, and C₂-C₆ alkynyl-R^{9a};

R^{9a} is selected from the group:

C₁-C₆ alkyl substituted with 0-3 R^{9b},
15 C₃-C₆ cycloalkyl substituted with 0-3 R^{9c},
aryl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and said heterocyclic group
20 is substituted with 0-3 R^{9c};

R^{9b} is selected from the group: phenyl, naphthyl, benzyl,
and 5-10 membered heterocyclic group consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and R^{9b} is substituted with 0-3
25 R^{9c};

R^{9c} is selected at each occurrence from the group:
CF₃, OCF₃, Cl, F, Br, I, =O, OH, phenyl, C(O)OR¹¹, NH₂,
30 NH(CH₃), N(CH₃)₂, -CN, NO₂;
C₁-C₄ alkyl substituted with 0-3 R^{9d},
C₁-C₄ alkoxy substituted with 0-3 R^{9d},
C₃-C₆ cycloalkyl substituted with 0-3 R^{9d},
aryl substituted with 0-5 R^{9d}, and
35 5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and said heterocyclic group
is substituted with 0-4 R^{9d};

5 R^{9d} is selected at each occurrence from the group:
C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃, OCF₃, Cl, F, Br, I, =O,
OH, phenyl, C(O)OR¹¹, NH₂, NH(CH₃), N(CH₃)₂, -CN, and
NO₂;

10 n is 1, 2, or 3; and

p is 1 or 2; and

q, at each occurrence, is independently 0, 1 or 2.

15

[4] In a further more preferred embodiment, the present
invention provides novel compounds of Formula II, wherein:

20 R¹⁰ is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, and C₁-C₆
alkyl substituted with 0-1 R^{10a};

R^{10a} is selected from the group: halo, -NO₂, -CN, -CF₃,
-CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹, -SR¹¹, -C(=NH)NH₂, and aryl
substituted with 0-1 R^{10b};

25

R^{10b} is selected from the group: -CO₂H, - NH₂, -OH, -SH, and
-C(=NH)NH₂;

R^{10c} is H or C₁-C₄ alkyl;

30

alternatively, R¹⁰ and R^{10c} can be combined to form a C₃-C₆
cycloalkyl group substituted with 0-1 R^{10a};

R¹¹ is, at each occurrence, independently H or C₁-C₄ alkyl;

35

R^{11a} is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₄ alkenyl,
C₂-C₄ alkynyl, aryl, aryl(C₁-C₄ alkyl)-,
C₃-C₆ cycloalkyl, or C₃-C₆ cycloalkyl(C₁-C₄ alkyl)-;

5 Q^2 is $-X-NR^{12}-Z$, $-NR^{12}-Y-Z$, or $-X-NR^{12}-Y-Z$;

X is selected from the group: $-C(=O)-$, $-S-$, $-S(=O)-$, and $-S(=O)_2-$;

10 Y is selected from the group: $-C(=O)-$, $-S-$, $-S(=O)-$, and $-S(=O)_2-$;

R^{12} is H or C_1-C_4 alkyl;

15 Z is C_1-C_4 haloalkyl,

C_1-C_4 alkyl substituted with 0-3 Z^a ,

C_2-C_4 alkenyl substituted with 0-3 Z^a ,

C_2-C_4 alkynyl substituted with 0-3 Z^a ,

C_3-C_{10} cycloalkyl substituted with 0-5 Z^b ,

20 C_3-C_{10} carbocycle substituted with 0-5 Z^b ,

aryl substituted with 0-5 Z^b ,

5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group:

O, S, and N, said heterocyclic group substituted

25 with 0-4 Z^b ;

an amino acid residue, or

$-A^7-A^8-A^9$;

Z^a is H, F, Cl, Br, I, $-NO_2$, $-CN$, $-NCS$, $-CF_3$, $-OCF_3$,

30 $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$,

$-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$,

C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl,

C_1-C_4 haloalkoxy,

35 C_3-C_{10} cycloalkyl substituted with 0-5 Z^b ,

C_3-C_{10} carbocycle substituted with 0-5 Z^b ,

aryl substituted with 0-5 Z^b , or

5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group:

5 O, S, and N, said heterocyclic group substituted
with 0-4 Z^b;

Z^b is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
-CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
10 -NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,
C₁-C₄ haloalkoxy,

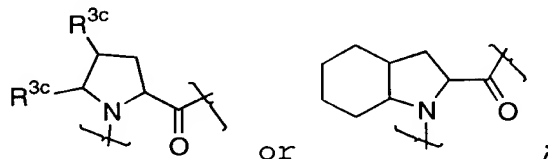
C₃-C₁₀ cycloalkyl substituted with 0-5 Z^c,
15 C₃-C₁₀ carbocycle substituted with 0-5 Z^c,
aryl substituted with 0-5 Z^c, or
5-10 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, said heterocyclic group substituted
20 with 0-4 Z^c;

Z^c is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
-CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
-NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
25 C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, or C₁-C₄
haloalkoxy;

R²⁰ is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, aryl,
aryl(C₁-C₄ alkyl)-, C₃-C₆ cycloalkyl, or
30 C₃-C₆ cycloalkyl(C₁-C₄ alkyl)-;

alternatively, NR²⁰R²⁰ may form a piperidinyl, piperazinyl,
or morpholinyl group;

35 A² is a bond, -NH-CR³R⁴-C(=O)-, an amino acid residue,



5

A³ is a bond or an amino acid residue;

A⁴ is a bond or an amino acid residue;

10 A⁵ is a bond;

R¹ is selected from the group: H,

C₁-C₆ alkyl substituted with 0-3 R^{1a},

C₂-C₆ alkenyl substituted with 0-3 R^{1a},

15 C₂-C₆ alkynyl substituted with 0-3 R^{1a}, and

C₃-C₆ cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:

20 Cl, F, Br, I, CF₃, CHF₂, OH, =O, SH, -CO₂R^{1b}, -SO₂R^{1b},
-SO₃R^{1b}, -P(O)₂R^{1b}, -P(O)₃R^{1b}, -C(=O)NHR^{1b}, -NHC(=O)R^{1b},
-SO₂NHR^{1b}, -OR^{1b}, -SR^{1b}, C₁-C₃ alkyl, C₃-C₆ cycloalkyl,

C₁-C₆ alkoxy, -S-(C₁-C₆ alkyl),

aryl substituted with 0-5 R^{1c},

-O-(CH₂)_q-aryl substituted with 0-5 R^{1c},

25 -S-(CH₂)_q-aryl substituted with 0-5 R^{1c}, and

5-10 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:

O, S, and N, and substituted with 0-3 R^{1c};

30 R^{1b} is H,

C₁-C₄ alkyl substituted with 0-3 R^{1c},

C₂-C₄ alkenyl substituted with 0-3 R^{1c},

C₂-C₄ alkynyl substituted with 0-3 R^{1c},

C₃-C₆ cycloalkyl substituted with 0-5 R^{1c},

35 C₃-C₆ carbocycle substituted with 0-5 R^{1c},

aryl substituted with 0-5 R^{1c}, or

5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:

5 O, S, and N, said heterocyclic group substituted
with 0-4 R^{1c};

R^{1c} is selected at each occurrence from: C₁-C₄ alkyl, Cl,
F, Br, I, OH, C₁-C₄ alkoxy, -CN, -NO₂, C(O)OR^{1d},
10 NR^{1d}R^{1d}, CF₃, and OCF₃;

R^{1d} is H or C₁-C₄ alkyl;

R² is H or C₁-C₄ alkyl;
15

R³ is selected from the group: H,
C₁-C₆ alkyl substituted with 0-4 R^{3a},
C₂-C₆ alkenyl substituted with 0-4 R^{3a},
C₂-C₆ alkynyl substituted with 0-4 R^{3a},
20 -(CH₂)_q-C₃-C₆ cycloalkyl substituted with 0-4 R^{3b},
-(CH₂)_q-aryl substituted with 0-5 R^{3b}, and
-(CH₂)_q-5-10 membered heterocyclic group consisting of
carbon atoms and 1-4 heteroatoms selected from
the group: O, S, and N, and said heterocyclic
25 group is substituted with 0-2 R^{3b};

R^{3a} is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹,
-SR¹¹, -C(=NH)NH₂, and aryl substituted with R^{10b};

30 R^{3b} is selected from the group: -CO₂H, -NH₂, -OH, -SH, and
-C(=NH)NH₂;

R^{3c} is, at each occurrence, independently selected from: H,
C₁-C₆ alkyl, -OH, and OR^{3d};

35 R^{3d} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
-(CH₂)_q-C₃-C₆ cycloalkyl, -(CH₂)_q-aryl, or
-(CH₂)_q-(5-10 membered heterocyclic group), wherein
said heterocyclic group consists of carbon atoms

5 and 1-4 heteroatoms selected from the group: O,
S, and N;

R^4 is selected from the group: H, C_1-C_6 alkyl, phenyl,
phenylmethyl-, phenylethyl-, C_3-C_6 cycloalkyl,
10 C_3-C_6 cycloalkylmethyl-, and C_3-C_6 cycloalkylethyl-;

R^9 is selected from the group: $-S(=O)_2R^{9a}$, $-C(=O)R^{9a}$,
 C_1-C_3 alkyl- R^{9a} , C_2-C_6 alkenyl- R^{9a} , and
 C_2-C_6 alkynyl- R^{9a} ;

15

R^{9a} is selected from the group:

C_1-C_6 alkyl substituted with 0-3 R^{9b} ,
 C_3-C_6 cycloalkyl substituted with 0-3 R^{9c} ,
aryl substituted with 0-3 R^{9c} , and
20 5-14 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and said heterocyclic group
is substituted with 0-3 R^{9c} ;

25 R^{9b} is selected from the group: phenyl, naphthyl, benzyl,
and 5-10 membered heterocyclic group consisting of
carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and R^{9b} is substituted with 0-3
 R^{9c} ;

30

R^{9c} is selected at each occurrence from the group:

CF_3 , OCF_3 , Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2 ,
 $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2 ;
 C_1-C_4 alkyl substituted with 0-3 R^{9d} ,
35 C_1-C_4 alkoxy substituted with 0-3 R^{9d} ,
 C_3-C_6 cycloalkyl substituted with 0-3 R^{9d} ,
aryl substituted with 0-5 R^{9d} , and
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the

5 group: O, S, and N, and said heterocyclic group
is substituted with 0-4 R^{9d};

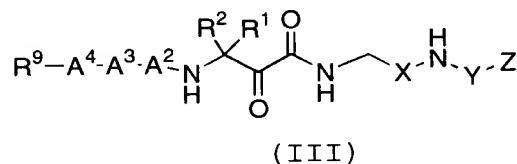
R^{9d} is selected at each occurrence from the group:
C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃, OCF₃, Cl, F, Br, I, =O,
10 OH, phenyl, C(O)OR¹¹, NH₂, NH(CH₃), N(CH₃)₂, -CN, and
NO₂;

n is 1 or 2; and

15 p is 1 or 2; and

q, at each occurrence, is independently 0, 1 or 2.

[5] In an even more preferred embodiment, the present
20 invention provides novel compounds of Formula III, wherein:



25 or a stereoisomer or pharmaceutically acceptable salt form
thereof, wherein;

R¹¹ is, at each occurrence, independently H or C₁-C₄ alkyl;

30 X is -C(=O)-, -S-, -S(=O)-, or -S(=O)₂-;

Y is -C(=O)- or -S(=O)₂-;

Z is C₁-C₄ haloalkyl,
35 C₁-C₄ alkyl substituted with 0-3 Z^a,
C₂-C₄ alkenyl substituted with 0-3 Z^a,
C₂-C₄ alkynyl substituted with 0-3 Z^a,
C₃-C₁₀ cycloalkyl substituted with 0-5 Z^b,

5 C₃-C₁₀ carbocycle substituted with 0-5 Z^b,
 aryl substituted with 0-5 Z^b, or
 5-10 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:
 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,
 10 pyrazinyl, piperazinyl, piperidinyl, imidazolyl,
 imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,
 morpholinyl, oxazolyl, oxazolidinyl,
 tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
 thiazolyl, triazinyl, triazolyl, benzimidazolyl,
 15 1H-indazolyl, benzofuranyl, benzothiofuranyl,
 benztetrazolyl, benzotriazolyl, benzisoxazolyl,
 benzoxazolyl, oxindolyl, benzoxazolinyl,
 benzthiazolyl, benzisothiazolyl, isatinoyl,
 isoquinolinyl, octahydroisoquinolinyl,
 20 tetrahydroisoquinolinyl, tetrahydroquinolinyl,
 isoxazolopyridinyl, quinazolinyl, quinolinyl,
 isothiazolopyridinyl, thiazolopyridinyl,
 oxazolopyridinyl, imidazolopyridinyl, and
 pyrazolopyridinyl; said heterocyclic group
 25 substituted with 0-4 Z^b;

Z^a is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
 -CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
 -NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
 30 C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,
 C₁-C₄ haloalkoxy,

C₃-C₁₀ cycloalkyl substituted with 0-5 Z^b,
 C₃-C₁₀ carbocycle substituted with 0-5 Z^b,
 35 aryl substituted with 0-5 Z^b, or
 5-10 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:
 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,
 pyrazinyl, piperazinyl, piperidinyl, imidazolyl,
 40 imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,

5 morpholinyl, oxazolyl, oxazolidinyl,
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
thiazolyl, triazinyl, triazolyl, benzimidazolyl,
1*H*-indazolyl, benzofuranyl, benzothiofuranyl,
benztetrazolyl, benzotriazolyl, benzisoxazolyl,
10 benzoxazolyl, oxindolyl, benzoxazolinyll,
benzthiazolyl, benzisothiazolyl, isatinoyl,
isoquinolinyl, octahydroisoquinolinyl,
tetrahydroisoquinolinyl, tetrahydroquinolinyl,
isoxazolopyridinyl, quinazolinyl, quinolinyl,
15 isothiazolopyridinyl, thiazolopyridinyl,
oxazolopyridinyl, imidazolopyridinyl, and
pyrazolopyridinyl; said heterocyclic group
substituted with 0-4 Z^b;

20 Z^b is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃,
-CH₃, -OCH₃, -CO₂R²⁰, -C(=O)NR²⁰R²⁰, -NHC(=O)R²⁰,
-NR²⁰R²⁰, -OR²⁰, -SR²⁰, -S(=O)R²⁰, -SO₂R²⁰, -SO₂NR²⁰R²⁰,
C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,
C₁-C₄ haloalkoxy,

25 C₃-C₁₀ cycloalkyl substituted with 0-5 Z^c,
C₃-C₁₀ carbocycle substituted with 0-5 Z^c,
aryl substituted with 0-5 Z^c, or
5-10 membered heterocyclic group consisting of carbon
30 atoms and 1-4 heteroatoms selected from the group:
pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,
pyrazinyl, piperazinyl, piperidinyl, imidazolyl,
imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,
morpholinyl, oxazolyl, oxazolidinyl,
35 tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
thiazolyl, triazinyl, triazolyl, benzimidazolyl,
1*H*-indazolyl, benzofuranyl, benzothiofuranyl,
benztetrazolyl, benzotriazolyl, benzisoxazolyl,
benzoxazolyl, oxindolyl, benzoxazolinyll,
40 benzthiazolyl, benzisothiazolyl, isatinoyl,
isoquinolinyl, octahydroisoquinolinyl,

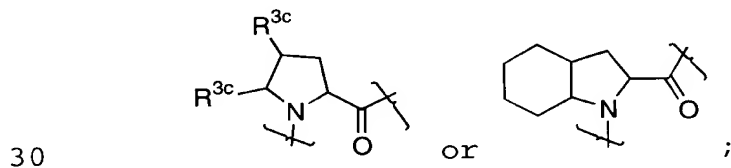
5 tetrahydroisoquinolinyl, tetrahydroquinolinyl,
isoxazolopyridinyl, quinazolinyl, quinolinyl,
isothiazolopyridinyl, thiazolopyridinyl,
oxazolopyridinyl, imidazolopyridinyl, and
pyrazolopyridinyl; said heterocyclic group
10 substituted with 0-4 Z^c ;

Z^c is H, F, Cl, Br, I, $-NO_2$, $-CN$, $-NCS$, $-CF_3$, $-OCF_3$,
 $-CH_3$, $-OCH_3$, $-CO_2R^{20}$, $-C(=O)NR^{20}R^{20}$, $-NHC(=O)R^{20}$,
 $-NR^{20}R^{20}$, $-OR^{20}$, $-SR^{20}$, $-S(=O)R^{20}$, $-SO_2R^{20}$, $-SO_2NR^{20}R^{20}$,
15 C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4
haloalkoxy;

R^{20} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl,
aryl(C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl, or
20 C_3-C_6 cycloalkyl(C_1-C_4 alkyl)-;

alternatively, $NR^{20}R^{20}$ may form a piperidinyl, piperazinyl,
or morpholinyl group;

25 A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, Ala, Arg, Asn, Asp, Aze,
Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu,
Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr,
Trp, Tyr, Val,



A^3 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln,
Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe,
Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;
35

5 A⁴ is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

R¹ is selected from the group: H,

10 C₁-C₆ alkyl substituted with 0-3 R^{1a},
C₂-C₆ alkenyl substituted with 0-3 R^{1a},
C₂-C₆ alkynyl substituted with 0-3 R^{1a}, and
C₃-C₆ cycloalkyl substituted with 0-3 R^{1a};

15 R^{1a} is selected at each occurrence from the group:

Cl, F, Br, I, CF₃, CHF₂, OH, =O, SH, -CO₂R^{1b}, -SO₂R^{1b},
-SO₃R^{1b}, -P(O)₂R^{1b}, -P(O)₃R^{1b}, -C(=O)NHR^{1b}, -NHC(=O)R^{1b},
-SO₂NHR^{1b}, -OR^{1b}, -SR^{1b}, C₁-C₃ alkyl, C₃-C₆ cycloalkyl,
C₁-C₆ alkoxy, -S-(C₁-C₆ alkyl),

20 aryl substituted with 0-5 R^{1c},

-O-(CH₂)_q-aryl substituted with 0-5 R^{1c},

-S-(CH₂)_q-aryl substituted with 0-5 R^{1c}, and

5-10 membered heterocyclic group consisting of carbon

atoms and 1-4 heteroatoms selected from the group:

25 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,
pyrazinyl, piperazinyl, piperidinyl, imidazolyl,
imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,
morpholinyl, oxazolyl, oxazolidinyl,

30 tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
thiazolyl, triazinyl, triazolyl, benzimidazolyl,
1H-indazolyl, benzofuranyl, benzothiofuranyl,

benztetrazolyl, benzotriazolyl, benzisoxazolyl,
benzoxazolyl, oxindolyl, benzoxazolinyl,
benzthiazolyl, benzisothiazolyl, isatinoyl,

35 isoquinolinyl, octahydroisoquinolinyl,
tetrahydroisoquinolinyl, tetrahydroquinolinyl,
isoxazolopyridinyl, quinazolinyl, quinolinyl,
isothiazolopyridinyl, thiazolopyridinyl,
oxazolopyridinyl, imidazolopyridinyl, and

40 pyrazolopyridinyl; and substituted with 0-3 R^{1c};

5

R^{1b} is H,

C₁-C₄ alkyl substituted with 0-3 R^{1c},

C₂-C₄ alkenyl substituted with 0-3 R^{1c},

C₂-C₄ alkynyl substituted with 0-3 R^{1c},

10 C₃-C₆ cycloalkyl substituted with 0-5 R^{1c},

C₃-C₆ carbocycle substituted with 0-5 R^{1c},

aryl substituted with 0-5 R^{1c}, or

5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:

15 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

pyrazinyl, piperazinyl, piperidinyl, imidazolyl,

imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,

morpholinyl, oxazolyl, oxazolidinyl,

tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,

20 thiazolyl, triazinyl, and triazolyl; said

heterocyclic group substituted with 0-3 R^{1c};

R^{1c} is selected at each occurrence from: C₁-C₄ alkyl, Cl,

F, Br, I, OH, C₁-C₄ alkoxy, -CN, -NO₂, C(O)OR^{1d},

25 NR^{1d}R^{1d}, CF₃, and OCF₃;

R^{1d} is H or C₁-C₄ alkyl;

R² is H or C₁-C₄ alkyl;

30

R³ is selected from the group: H,

C₁-C₆ alkyl substituted with 0-4 R^{3a},

C₂-C₆ alkenyl substituted with 0-4 R^{3a},

C₂-C₆ alkynyl substituted with 0-4 R^{3a},

35 -(CH₂)_q- C₃-C₆ cycloalkyl substituted with 0-4 R^{3b},

-(CH₂)_q-aryl substituted with 0-5 R^{3b}, and

-(CH₂)_q-5-10 membered heterocyclic group consisting of
carbon atoms and 1-4 heteroatoms selected from
the group: pyridinyl, furanyl, thienyl, pyrrolyl,

5 pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,
imidazolyl, imidazolidinyl, indolyl, tetrazolyl,
isoxazolyl, morpholynyl, oxazolyl, oxazolidinyl,
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
thiazolyl, triazinyl, triazolyl, benzimidazolyl,
10 1H-indazolyl, benzofuranyl, benzothiofuranyl,
benztetrazolyl, benzotriazolyl, benzisoxazolyl,
benzoxazolyl, oxindolyl, benzoxazolynyl,
benzthiazolyl, benzisothiazolyl, isatinoyl,
isoquinolynyl, octahydroisoquinolynyl,
15 tetrahydroisoquinolynyl, tetrahydroquinolynyl,
isoxazolopyridinyl, quinazolynyl, quinolynyl,
isothiazolopyridinyl, thiazolopyridinyl,
oxazolopyridinyl, imidazolopyridinyl, and
pyrazolopyridinyl; and said heterocyclic group is
20 substituted with 0-2 R^{3b};

R^{3a} is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹,
-SR¹¹, -C(=NH)NH₂, and aryl substituted with R^{10b};

25 R^{3b} is selected from the group: -CO₂H, - NH₂, -OH, -SH, and
-C(=NH)NH₂;

R^{3c} is, at each occurrence, independently selected from: H,
C₁-C₆ alkyl, -OH, and OR^{3d};

30 R^{3d} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
-(CH₂)_q- C₃-C₆ cycloalkyl, -(CH₂)_q-aryl, or
-(CH₂)_q-(5-10 membered heterocyclic group), wherein
said heterocyclic group consists of carbon atoms
and 1-4 heteroatoms selected from the group: O,
35 S, and N;

R⁴ is selected from the group: H, C₁-C₆ alkyl, phenyl,
phenylmethyl-, phenylethyl-, C₃-C₆ cycloalkyl,
40 C₃-C₆ cycloalkylmethyl-, and C₃-C₆ cycloalkylethyl-;

5

R^9 is selected from $-S(=O)_2R^{9a}$ and $-C(=O)R^{9a}$;

R^{9a} is selected from the group:

phenyl substituted with 0-3 R^{9c} ,
 10 naphthyl substituted with 0-3 R^{9c} , and
 5-14 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the
 group: pyridinyl, furanyl, thienyl, pyrrolyl,
 pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,
 15 imidazolyl, imidazolidinyl, indolyl, tetrazolyl,
 isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,
 tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
 thiazolyl, triazinyl, triazolyl, benzimidazolyl,
 1H-indazolyl, benzofuranyl, benzothiofuranyl,
 20 benztetrazolyl, benzotriazolyl, benzisoxazolyl,
 benzoxazolyl, oxindolyl, benzoxazolinyl,
 benzthiazolyl, benzisothiazolyl, isatinoyl,
 isoquinolinyl, octahydroisoquinolinyl,
 tetrahydroisoquinolinyl, tetrahydroquinolinyl,
 25 isoxazolopyridinyl, quinazolinyl, quinolinyl,
 isothiazolopyridinyl, thiazolopyridinyl,
 oxazolopyridinyl, imidazolopyridinyl, and
 pyrazolopyridinyl; and said heterocyclic group is
 substituted with 0-3 R^{9c} ;

30

R^{9c} is selected at each occurrence from the group:

CF_3 , OCF_3 , Cl, F, Br, I, =O, OH, phenyl, $C(O)OR^{11}$, NH_2 ,
 $NH(CH_3)$, $N(CH_3)_2$, -CN, NO_2 ;

C_1-C_4 alkyl substituted with 0-3 R^{9d} ,

35

C_1-C_4 alkoxy substituted with 0-3 R^{9d} ,

C_3-C_6 cycloalkyl substituted with 0-3 R^{9d} ,

aryl substituted with 0-5 R^{9d} , and

5-6 membered heterocyclic group consisting of carbon

atoms and 1-4 heteroatoms selected from the

40

group: pyridinyl, furanyl, thienyl, pyrrolyl,

5 pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,
imidazolyl, imidazolidinyl, indolyl, tetrazolyl,
isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
thiazolyl, triazinyl, and triazolyl; said
10 heterocyclic group is substituted with 0-4 R^{9d};

R^{9d} is selected at each occurrence from the group:

C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃, OCF₃, Cl, F, Br, I, =O,
OH, phenyl, C(O)OR¹¹, NH₂, NH(CH₃), N(CH₃)₂, -CN, and
15 NO₂;

p is 1 or 2; and

q, at each occurrence, is independently 0, 1 or 2.
20

[6] In a further even more preferred embodiment, the
present invention provides novel compounds of Formula III,
wherein:

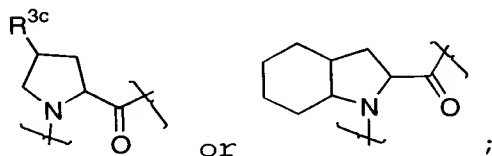
25 X is -C(=O)-;

Y is -S(=O)₂-;

Z is selected from the group:

30 methyl, ethyl, propyl, trifluoromethyl,
phenyl, benzyl, 4-phenyl-phenyl, 4-NCS-phenyl,
2-fluorophenyl-, 3-fluorophenyl-, 4-fluorophenyl-,
2-chlorophenyl-, 3-chlorophenyl-, 4-chlorophenyl-,
2-cyanophenyl-, 3-cyanophenyl-, 4-cyanophenyl-,
35 2-nitrophenyl-, 3-nitrophenyl-, 4-nitrophenyl-,
2-CF₃SO₂-phenyl-, 3-CF₃SO₂-phenyl-, 4-CF₃SO₂-phenyl-,
2-CF₃-phenyl-, 3-CF₃-phenyl-, 4-CF₃-phenyl-,
3-NO₂-4-Cl-phenyl-, 3-Cl-4-CH₃-phenyl-,
2-Cl-5-CF₃-phenyl-, 2-Cl-5-CO₂H-phenyl-,
40 3-NO₂-4-CH₃-phenyl-, 3-Cl-5-NH₂SO₂-phenyl-,
3,5-diCF₃-phenyl-, 3,4-diCF₃-phenyl-,

- 5 3,5-diCl-phenyl-, 2,5-diCl-phenyl-, 3,4-diCl-phenyl-,
 3,5-diF-phenyl-, 2,5-diF-phenyl-, 3,4-diF-phenyl-,
 2-F-4-Cl-5-CO₂H-phenyl-, 2,4-diCl-5-CO₂H-phenyl-,
 2,4-diCl-5-CH₃CO₂-phenyl-, 2,4-diCl-5-CH₃-phenyl-,
 2-OH-3,5-diCl-phenyl-, 2,4,5-triCl-phenyl-,
 10 3,5-diCl-4-(4-NO₂phenyl)phenyl-,
 2-Cl-5-benzylNHCO-phenyl-, 2-Cl-5-CF₃CH₂NHCO-phenyl-,
 2-Cl-5-cyclopropylmethylNHCO-phenyl-,
 2-Cl-4-CH₃CONH-phenyl-, 3-Cl-5-(phenylCONHSO₂)-phenyl-,
 3-Cl-5-CH₃CONH-phenyl-, 5-ethoxy-benzothiazol-2-yl,
 15 naphth-2-yl, (CH₃CONH)thiadiazolyl-,
 (s-butylCONH)thiadiazolyl-, (n-pentylCONH)thiadiazolyl-,
 (phenylCONH)thiadiazolyl-, and
 (3-ClphenylCONH)thiadiazolyl-;
- 20 A² is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln,
 Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe,
 Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, Val;



- 25 A³ is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln,
 Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe,
 Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;
- 30 A³ is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln,
 Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe,
 Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

R¹ is selected from the group:

- 35 -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH₂CH₂CH₃,
 -CH₂CH(CH₃)₂, -CH₂C(CH₃)₃, -CH₂CH₂C(CH₃)₃,
 -CH₂CH₂CH₂C(CH₃)₃, -CH₂CH₂CH₂CH(CH₃)₂,
 -CH₂CH₂CH₂CH(CH₂CH₃)₂, -CH₂CH₂CH₂CH₂CH₃,

5 $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$,
 $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CHF}_2$,
 $-\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}=\text{CHCH}_3$, *cis*- $\text{CH}_2\text{CH}=\text{CH}(\text{CH}_3)$,
 trans- $\text{CH}_2\text{CH}=\text{CH}(\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$, $-\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$,
 10 $-\text{CH}_2\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)_2$,
 $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{C}(\text{CH}_3)_3$,
 $-\text{CH}_2\text{CH}_2\text{CO}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$,
 phenyl, benzyl, phenethyl, phenpropyl, phenbutyl,
 (2-methylphenyl)ethyl-, (3-methylphenyl)ethyl-,
 15 (4-methylphenyl)ethyl-, (4-ethylphenyl)ethyl-,
 (4-*i*-propylphenyl)ethyl-, (4-*t*-butylphenyl)ethyl-,
 (4-hydroxyphenyl)ethyl-, (4-phenyl-phenyl)ethyl-,
 (4-phenoxy-phenyl)ethyl-, (4-cyclohexyl-phenyl)ethyl-,
 (4-cyclopropyl-phenyl)ethyl-,
 20 (2,5-dimethylphenyl)ethyl-,
 (2,4-dimethylphenyl)ethyl-, (2,6-difluorophenyl)ethyl-,
 (4-cyclopentyl-phenyl)ethyl-,
 (4-cyclobutyl-phenyl)ethyl-,
 (2-trifluoromethylphenyl)ethyl-,
 25 (3-trifluoromethylphenyl)ethyl-,
 (4-trifluoromethylphenyl)ethyl-,
 (2-fluorophenyl)ethyl-, (3-fluorophenyl)ethyl-,
 (4-fluorophenyl)ethyl-, (2-chlorophenyl)ethyl-,
 (3-chlorophenyl)ethyl-, (4-chlorophenyl)ethyl-,
 30 (2-bromophenyl)ethyl-, (3-bromophenyl)ethyl-,
 (4-bromophenyl)ethyl-,
 (2,3,4,5,6-pentafluorophenyl)ethyl-,
 (naphth-2-yl)ethyl, (cyclobutyl)methyl,
 (cyclobutyl)ethyl, (cyclobutyl)propyl, cyclopropyl,
 35 cyclobutyl, cyclopentyl, and cyclohexyl;

R^2 is H, methyl or ethyl;

40 R^{3c} is H, methyl, ethyl, -OH, methoxy, ethoxy, propoxy,
 phenoxy, or benzyloxy; and

R^9 is selected from:

5 2-pyrazinyl-carbonyl-,
 4-(N-pyrrolyl)phenyl-carbonyl-,
 5-(4-chlorophenyl)furan-2-yl-carbonyl-,
 1-anthracenyl-carbonyl-,
 7-nitro-anthracen-1-yl-carbonyl-,
 10 (3-phenyl-2-cyanomethoxyphenyl)carbonyl-,
 5-(2-Cl-3-CF₃-phenyl)-furan-2-yl-carbonyl-,
 5-(4-Cl-phenyl)-furan-2-yl-carbonyl-,
 5-(pyrid-2-yl)-thiophen-2-yl-carbonyl-,
 (2-methoxyphenyl)ethylcarbonyl-,
 15 (3-benzopyrrolyl)ethylcarbonyl-,
 (N-phenyl-5-propyl-imidazol-4-yl)-carbonyl-,
 1-naphthyl-sulphonyl-, and
 5-(isoxazol-2-yl)thiophen-2-yl-sulphonyl-.

20 [7] In most preferred embodiment, the compound of Formula
 (I) is selected from the group:

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
 L-alanyl-2-oxo-(3 S)-3-amino pentanoylglycine;

25 (3S)-2-oxo-3-{[N-(2-pyrazinylcarbonyl)-L-leucyl-L-
 isoleucyl-3-cyclohexyl-L-alanyl]amino}-N-(2H-tetrazol-5-
 ylmethyl) pentanamide;

30 2-oxo-3-[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
 cyclohexylalanyl]amino]-N-(sulfomethyl)pentanamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
 cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(2-nitrophenyl)
 35 sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
 cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(methylsulfonyl)
 40 glycinamide;

5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(phenylmethyl)sulfonyl]glycinamide;

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(phenylsulfonyl)glycinamide;

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(trifluoromethyl)sulfonyl]glycinamide;

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-nitrophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-nitrophenyl)sulfonyl]glycinamide;

25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-fluorophenyl)sulfonyl]glycinamide;

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-fluorophenyl)sulfonyl]glycinamide;

35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-fluorophenyl) sulfonyl]glycinamide;

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chlorophenyl) sulfonyl]glycinamide;

5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3-chlorophenyl) sulfonyl]glycinamide;

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-(thionitroso) phenyl]sulfonyl]glycinamide;

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-[(trifluoromethyl) sulfonyl]phenyl]sulfonyl]glycinamide;

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-(trifluoromethyl)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-cyanophenyl) sulfonyl]glycinamide;

25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3-chloro-4-methylphenyl) sulfonyl]glycinamide;

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chloro-3-nitrophenyl) sulfonyl]glycinamide;

35 N-(2-pyrazinylcarbonyl)-L-leucyl-L- isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichlorophenyl) sulfonyl]glycinamide;

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-methyl-3-nitrophenyl) sulfonyl]glycinamide;

5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-(trifluoromethyl)phenyl]sulfonyl]glycinamide;

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide;

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2,5-dichlorophenyl)sulfonyl]glycinamide;

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,4-difluorophenyl)sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]glycinamide;

25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[(2,4,5-trichlorophenyl)-sulfonyl]glycinamide;

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(5-carboxy-4-chloro-2-fluorophenyl)sulfonyl]glycinamide;

35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]glycinamide;

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(2-naphthalenylsulfonyl)glycinamide;

5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[(4-
(phenyl)phenyl)-sulfonyl]glycinamide;

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(6-ethoxy-2-
benzothiazolyl)sulfonyl]glycinamide;

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[[2-chloro-5-
[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[(2-
trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide;

25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-
[(cyclopropylmethyl)amino]carbonyl]phenyl]sulfonyl]
glycinamide;

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-nitro-4-(2-
pyrimidinylthio)phenyl]sulfonyl]glycinamide;

35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-4-
(acetylamino)phenyl]sulfonyl]glycinamide;

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-chloro-4-(2-
benzoxazolylthio)phenyl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[[3,5-dichloro-4-
(4-nitrophenoxy)phenyl]sulfonyl]glycinamide;

5 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]glycinamide;

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-cyanophenyl)sulfonyl]glycinamide;

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3-(aminosulfonyl)-5-chlorophenyl]sulfonyl]glycinamide;

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[[3,5-bis(trifluoromethyl)phenyl]sulfonyl]glycinamide;

25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[4-[5-[3-(4-chlorophenyl)-3-oxo-1-propenyl]-2-furanyl]phenyl]sulfonyl]glycinamide;

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[[(phenylmethyl) amino] carbonyl]phenyl]sulfonyl]glycinamide;

35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[[(2,2,2-trifluoroethyl) amino] carbonyl]phenyl]sulfonyl]glycinamide;

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[(benzoylamino)sulfonyl]-5-chlorophenyl]sulfonyl]glycinamide;

45 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine;

5 (3S)-5,5-difluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N-(2H-tetrazol-5-ylmethyl)pentanamide;

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide;

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide;

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-(3-aminosulfonyl-5-chlorophenyl)sulfonyl]glycinamide;

25 (3S)-5,5,5-trifluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N-(2H-tetrazol-5-ylmethyl)pentanamide;

30 N-[4-sec-butyl-15-[(3-chloro-5-[(3,3,3-trifluoropropanoyl)amino]sulfonyl]phenyl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

35 N-[4-sec-butyl-15-[(3-chloro-5-[(hexanoylamino)sulfonyl]phenyl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

40 N-[15-[(1,1'-biphenyl)-3-ylsulfonyl]amino]-4-sec-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-

5 hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-
pyrazinecarboxamide;

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-15-
{[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]amino}-
10 2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-
pyrazinecarboxamide;

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-15-{[(3',5'-
dichloro[1,1'-biphenyl]-4-yl)sulfonyl]amino}-10-ethyl-1-
15 isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-
1-yl)-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-{[(4'-chloro[1,1'-biphenyl]-3-
yl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-
20 difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-
tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-
1-isobutyl-15-({[3-(2-methylphenoxy)phenyl]sulfonyl}amino)-
25 2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-
pyrazinecarboxamide;

N-[4-*sec*-butyl-15-({[3-(2-
chlorophenoxy)phenyl]sulfonyl}amino)-7-(cyclohexylmethyl)-
30 10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-
3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13-pentaoxo-1-
35 (2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid;

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-
1-isobutyl-15-{[(4'-methyl[1,1'-biphenyl]-3-
yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-
40 tetraazapentadec-1-yl)-2-pyrazinecarboxamide;

- 5 *N*-[15-({[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl)sulfonyl}amino)-4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 10 *N*-[4-*sec*-butyl-15-[(5-[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 15 *N*-[4-*sec*-butyl-15-[(5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 20 *N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[(5-[(4-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 25 *N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[(5-[(3-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 30 *N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[(5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 35 *N*-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-15-[(3-phenoxyphenyl)sulfonyl]amino)-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;
- 40 6-*sec*-butyl-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-1,4,7,10,13-pentaaxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid;

5

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[(5-[(3-methylbutanoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

10

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-([5-(hexanoylamino)-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

15

methyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate;

20

N-[4-*sec*-butyl-15-[(3-chloro-5-[(3-chlorobenzoyl)amino]sulfonyl]phenyl)sulfonyl]amino)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

25

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-15-([4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl)sulfonyl]amino)-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

30

N-[15-([1,1'-biphenyl]-3-ylsulfonyl)amino]-4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

35

N-[4-*sec*-butyl-15-[(5-[(4-*tert*-butylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

40

5 *N*-[4-*sec*-butyl-15-{{(3-chloro-5-{{(3-methylbutanoyl) amino} sulfonyl} phenyl) sulfonyl} amino}-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

10

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-14-[4-(4-methoxyphenyl)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-3-yl]-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-

15 tetraazatetradec-1-yl}-2-pyrazinecarboxamide;

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[(5-[(4-ethylbenzoyl) amino]-1,3,4-thiadiazol-2-yl) sulfonyl] amino}-1-isobutyl-2,5,8,11,12,15-hexaoxo-20 3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-[(5-[(4-chlorobenzoyl) amino]-1,3,4-thiadiazol-2-yl) sulfonyl] amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-25 3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-15-[(5-[(3,5-difluorobenzoyl) amino]-1,3,4-thiadiazol-2-yl) sulfonyl] amino]-10-(2,2-difluoroethyl)-1-isobutyl-30 2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-[4-*sec*-butyl-15-[(5-[(3-chlorobenzoyl) amino]-1,3,4-thiadiazol-2-yl) sulfonyl] amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-35 3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide;

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-40 tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide;

5 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-yn-1-yl}-2-pyrazinecarboxamide;

10 *tert*-butyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate;

15 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-14-phenyl-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide

20 *N*-((1*S*)-1-[[[(1*S*,2*R*)-1-[[[(1*S*)-1-(cyclohexylmethyl)-2-[[[(1*S*)-1-ethyl-2,3-dioxo-3-(1-pyrrolidinyl)propyl]amino]-2-oxoethyl)amino]carbonyl]-2-methylbutyl)amino]carbonyl]-3-methylbutyl)-2-pyrazinecarboxamide;

25 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-15,15,15-trifluoro-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

30 *N*-{(1*S*,4*S*,7*S*,10*S*)-15-amino-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide;

35 (3*S*,6*S*,9*S*,12*S*,16*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-16-methyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oic acid;

40 *N*-[9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-2,5,8,11,14-pentaoxo-14-(2-pyrazinyl)-4,7,10,13-tetraazatetradec-1-anoyl]aspartic acid;

40 (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaooctadecan-18-oic acid;

5

1,1-dimethylethyl N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine;

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine;

(4R)-1-[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl]-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H)-tetrazol-5-yl methyl) amino]propyl]-4-(phenylmethoxy)-L-prolinamide;

(4R)-N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-3-methoxy-2,3-dioxopropyl]-4-(phenylmethoxy)-L-prolinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide;

25 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide;

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-acetylamino)1,3,4-thiadiazol-2-yl)sulfonyl]glycinamide;

35 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[3,5-dichlorophenyl)sulfonyl]glycinamide;

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-

5 aminopentanoyl N-(4-methyl-3-nitrophenyl)sulfonyl]-
glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-
(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-
10 aminopentanoyl N-(3-carboxyl-4-chloro-2-
fluorophenyl)sulfonyl]-glycinamide;

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-
(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-
15 aminopentanoyl N-[(3-chloro-4-acetylamino)phenyl]sulfonyl]-
glycinamide;

N-((1S)-1-[[[(1S,2R)-1-[[[(2S,4R)-2-([[(1S)-3-((2-[[[(3-
[(benzoylamino)sulfonyl]-5-chlorophenyl)sulfonyl]amino)-2-
20 oxoethyl]amino)-1-(2,2-difluoroethyl)-2,3-
dioxopropyl]amino}carbonyl)-4-
(benzyloxy)pyrrolidinyl]carbonyl}-2-
methylbutyl]amino]carbonyl}-3-methylbutyl)-2-
pyrazinecarboxamide;

25 *tert*-butyl ((3S)-3-[[[(2S,4R)-4-(benzyloxy)-1-[(2S)-3-
methyl-2-((2S)-3-methyl-2-[(2-
pyrazinylcarbonyl)amino]butanoyl]amino)butanoyl]pyrrolidiny
l]carbonyl]amino]-5,5-difluoro-2-
30 oxopentanoyl]amino)acetate;

N-((1S)-1-[[[(1S,2R)-1-[[[(2S,4R)-4-(benzyloxy)-2-([[(1S)-3-
[(2-[[[(3-chloro-4-methylphenyl)sulfonyl]amino]-2-
oxoethyl]amino)-1-(2,2-difluoroethyl)-2,3-
35 dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-
methylbutyl]amino]carbonyl}-3-methylbutyl)-2-
pyrazinecarboxamide;

N-((1S)-1-[[[(1S,2R)-1-[[[(2S,4R)-4-(benzyloxy)-2-([[(1S)-3-
40 ((2-[[[(5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-
yl)sulfonyl]amino)-2-oxoethyl]amino)-1-(2,2-difluoroethyl)-
2,3-dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl}-2-

5 methylbutyl)amino]carbonyl}-3-methylbutyl)-2-
pyrazinecarboxamide;

methyl ({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-
methyl-2-({(2*S*)-4-methyl-2-[(2-
10 pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]pyrrolidi
nyl}carbonyl)amino]-5,5-difluoro-2-
oxopentanoyl)amino)acetate;

N-{(1*S*)-1-[({(1*S*,2*R*)-1-[({(2*S*,4*R*)-4-(benzyloxy)-2-({(1*S*)-3-
15 [(2-[((2,4-dichloro-5-methylphenyl)sulfonyl]amino)-2-
oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-
dioxopropyl]amino}carbonyl)pyrrolidinyl}carbonyl)-2-
methylbutyl)amino]carbonyl}-3-methylbutyl)-2-
pyrazinecarboxamide;

20 *N*-[(1*S*)-1-({[(1*S*,2*R*)-1-({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-
(2,2-difluoroethyl)-3-[(2-[((3,4-
difluorophenyl)sulfonyl]amino)-2-oxoethyl)amino]-2,3-
dioxopropyl]amino)carbonyl]pyrrolidinyl}carbonyl)-2-
25 methylbutyl]amino}carbonyl)-3-methylbutyl]-2-
pyrazinecarboxamide;

methyl 5-({[({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-
methyl-2-({(2*S*)-4-methyl-2-[(2-
30 pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]pyrrolidi
nyl}carbonyl)amino]-5,5-difluoro-2-
oxopentanoyl)amino)acetyl]amino)sulfonyl)-2,4-
dichlorobenzoate;

35 *N*-{(1*S*)-1-[({(1*S*,2*R*)-1-[({(2*S*,4*R*)-4-(benzyloxy)-2-({(1*S*)-1-
(2,2-difluoroethyl)-3-[(2-[((4-(3,5-dimethyl-1-
piperidinyl)-3-nitrophenyl)sulfonyl]amino)-2-
oxoethyl]amino)-2,3-
dioxopropyl]amino]carbonyl}pyrrolidinyl)carbonyl]-2-
40 methylbutyl]amino)carbonyl]-3-methylbutyl)-2-
pyrazinecarboxamide;

5 N-[(1S)-1-({[(1S,2R)-1-({(2S,4R)-4-(benzyloxy)-2-({[(1S)-1-(2,2-difluoroethyl)-3-[(2-({[3-nitrophenyl)sulfonyl]amino}-2-oxoethyl)amino]-2,3-dioxopropyl)amino)carbonyl]pyrrolidinyl)carbonyl)-2-methylbutyl]amino)carbonyl)-3-methylbutyl]-2-pyrazinecarboxamide;

10 N-[(1S)-1-({[(1S,2R)-1-({(2S,4R)-4-(benzyloxy)-2-({[(1S)-1-(2,2-difluoroethyl)-3-({[2-({[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-2-oxoethyl]amino}-2,3-dioxopropyl)amino]carbonyl]pyrrolidinyl)carbonyl)-2-methylbutyl]amino)carbonyl)-3-methylbutyl]-2-pyrazinecarboxamide;

20 5-({[({[3S)-3-({[(2S,4R)-4-(benzyloxy)-1-[(2S,3R)-3-methyl-2-({[(2S)-4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]pyrrolidinyl)carbonyl)amino]-5,5-difluoro-2-oxopentanoyl]amino)acetyl]amino)sulfonyl)-2,4-dichlorobenzoic acid;

25 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoylglycine;

30 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(trifluoromethyl)sulfonyl]glycinamide;

35 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide;

40 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3-nitrophenyl)sulfonyl]glycinamide;

5 (4R)-1-[[5-(4-chlorophenyl)-2-furanyl]carbonyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H-tetrazol-5-ylmethyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide;

(2S,4R)-4-(benzyloxy)-N-{(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H-tetraazol-5-ylmethyl)amino]propyl}-1-((2S,3R)-3-methyl-2-[[9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

15 tert-butyl {[(3S)-3-([(2S,4R)-4-(benzyloxy)-1-((2S,3R)-3-methyl-2-[[9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl)carbonyl]amino)-5,5-difluoro-2-oxopentanoyl]amino}acetate;

20 {[(3S)-3-([(2S,4R)-4-(benzyloxy)-1-((2S,3R)-3-methyl-2-[[9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl)carbonyl]amino)-5,5-difluoro-2-oxopentanoyl]amino}acetic acid;

(2S,4R)-N-[(1S)-3-{[2-([5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl)amino]-2-oxoethyl]amino}-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2S,3R)-3-methyl-2-[[9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

30 (2S,4R)-4-(benzyloxy)-N-[(1S)-1-(2,2-difluoroethyl)-3-{[2-([5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl)amino]-2-oxoethyl]amino}-2,3-dioxopropyl]-1-((2S,3R)-3-methyl-2-[[9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

35 ((2S,4R)-4-(benzyloxy)-N-[(1S)-3-({2-([5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)amino]-2-oxoethyl]amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-((2S,3R)-3-methyl-2-[[9-oxo-9H-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

40

5 (2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-1-(2,2-difluoroethyl)-3-({2-
[({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-
yl)sulfonyl)amino]-2-oxoethyl}amino)-2,3-dioxopropyl]-1-
(2*S*,3*R*)-3-methyl-2-[(9-oxo-9*H*-fluoren-1-
yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide;

10 *tert*-butyl {[(3*S*)-3-({ [(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-
{ [5-(4-chlorophenyl)-2-furoyl]amino}-3-
methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-
2-oxopentanoyl]amino}acetate;

15 {[(3*S*)-3-({ [(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-
{ [5-(4-chlorophenyl)-2-furoyl]amino}-3-
methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-
2-oxopentanoyl]amino}acetic acid;

20 (2*S*,4*R*)-*N*-[(1*S*)-3-{{2-({ [5-(acetylamino)-1,3,4-thiadiazol-
2-yl]sulfonyl}amino)-2-oxoethyl}amino}-1-(2,2-
difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-2-
{ [5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-
25 pyrrolidinecarboxamide;

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-([(5-[(3-
chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-
2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-
30 ((2*S*,3*R*)-2-([5-(4-chlorophenyl)-2-furoyl]amino)-3-
methylpentanoyl)-2-pyrrolidinecarboxamide;

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-([[1,1'-biphenyl]-3-
ylsulfonyl]amino)-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-
35 2,3-dioxopropyl]-1-((2*S*,3*R*)-2-([5-(4-chlorophenyl)-2-
furoyl]amino)-3-methylpentanoyl)-2-pyrrolidinecarboxamide;

N-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-
[(1*R*)-1-methylpropyl]-2,5,8,11,12-penta-3,6,9,13-
40 tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide;

- 5 (6*S*,9*S*,12*S*)-*N*,3-diallyl-6-(cyclohexylmethyl)-12-isobutyl-9-
[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-
4,7,10,13-tetraazahexadecan-1-amide;
- (4*S*,7*S*,10*S*)-*N*,13-diallyl-10-(cyclohexylmethyl)-4-isobutyl-
10 7-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-3,6,9,12-
tetraazapentadecan-15-amide;
- N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-
15 tetraazahexadec-15-en-1-yl}-2-pyridinecarboxamide;
- N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-
20 tetraazahexadec-15-en-1-yl}nicotinamide;
- N*-{(1*S*,4*S*,7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-
[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-
25 tetraazahexadec-15-en-1-yl}-4-nitro-1*H*-pyrazole-3-
carboxamide;
- 2-{(3*S*,6*S*,9*S*)-12-allyl-9-(cyclohexylmethyl)-3-isobutyl-6-
[(1*R*)-1-methylpropyl]-4,7,10,13,14-pentaoxo-2,5,8,11,15-
pentaazaoctadec-17-en-1-anoyl}benzoic acid;
- 30 *N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-
2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-
yl]nicotinamide;
- N*-allyl-9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-
35 isobutyl-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-
tetraazahexadecan-1-amide;
- {(3-[(1-[3-methyl-2-({4-methyl-2-[(2-
pyrazinylcarbonyl)amino]pentanoyl)amino]pentanoyl]-
40 octahydro-1*H*-indol-2-yl)carbonyl)amino]-2-
oxopentanoyl)amino}acetic acid;

5 *tert*-butyl ({3-[(1-[3-methyl-2-({4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl}amino)-pentanoyl]octahydro-1*H*-indol-2-yl}carbonyl)amino]-2-oxopentanoyl}amino)acetate; and

10 (3*S*,6*S*,9*S*,12*S*)-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-9-[(1*R*)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-oic acid;

or a pharmaceutically acceptable salt form thereof.

15

[8] In another preferred embodiment, the present invention provides novel compounds of Formula I, wherein:

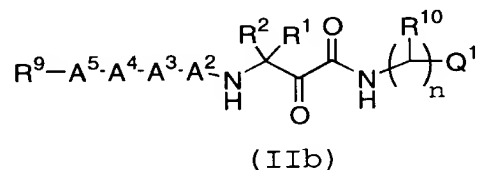
Q is $-(CR^{10}R^{10c})_n-Q^1$ or

20

an amino acid residue, wherein the amino acid residue comprises a natural, a modified or an unnatural amino acid.

25

[9] In a more preferred embodiment, the present invention provides novel compounds of Formula IIb, wherein:



30 or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

R^{10} is selected from the group: $-CO_2R^{11}$, $-NR^{11}R^{11}$, and C_1-C_6 alkyl substituted with 0-1 R^{10a} ;

35

R^{10a} is selected from the group: halo, $-NO_2$, $-CN$, $-CF_3$, $-CO_2R^{11}$, $-NR^{11}R^{11}$, $-OR^{11}$, $-SR^{11}$, $-C(=NH)NH_2$, and aryl substituted with 0-1 R^{10b} ;

5 R^{10b} is selected from the group: -CO₂H, -NH₂, -OH, -SH, and
-C(=NH)NH₂;

R^{10c} is H or C₁-C₄ alkyl;

10 alternatively, R¹⁰ and R^{10c} can be combined to form a C₃-C₆
cycloalkyl group substituted with 0-1 R^{10a};

R¹¹ is, at each occurrence, independently H or C₁-C₄ alkyl;

15 R^{11a} is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₄ alkenyl,
C₂-C₄ alkynyl, aryl, aryl(C₁-C₄ alkyl)-,
C₃-C₆ cycloalkyl, or C₃-C₆ cycloalkyl(C₁-C₄ alkyl)-;

Q¹ is selected from:

20 -CO₂R¹¹, -SO₂R¹¹, -SO₃R¹¹, -P(O)₂R¹¹, -P(O)₃R¹¹,
aryl substituted with 0-4 Q^{1a}, and
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, said heterocyclic group substituted
25 with 0-4 Q^{1a};

Q^{1a} is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃, -CH₃,
-OCH₃, -CO₂R¹⁹, -C(=O)NR¹⁹R¹⁹, -NHC(=O)R¹⁹, -SO₂R¹⁹,
-SO₂NR¹⁹R¹⁹, -NR¹⁹R¹⁹, -OR¹⁹, -SR¹⁹, C₁-C₄ alkyl, C₁-C₄
30 alkoxy, C₁-C₄ haloalkyl, or C₁-C₄ haloalkoxy;

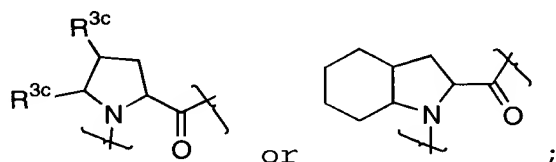
R¹⁹ is C₁-C₄ alkyl, C₁-C₄ haloalkyl, aryl, aryl(C₁-C₄
alkyl), C₃-C₆ cycloalkyl, or C₃-C₆ cycloalkyl(C₁-C₄
alkyl);

35

alternatively, NR¹⁹R¹⁹ may form a 5-6 membered heterocyclic
group consisting of carbon atoms, a nitrogen atom, and
optionally a second heteroatom selected from the
group: O, S, and N;

5

A² is a bond, -NH-CR³R⁴-C(=O)-, an amino acid residue,



10

A³ is a bond, -NH-CR⁵R⁶-C(=O)-, or an amino acid residue;

A⁴ is a bond, -NH-CR⁷R⁸-C(=O)-, or an amino acid residue;

A⁵ is a bond or an amino acid residue;

15 A⁷ is a bond or an amino acid residue;

A⁸ is an amino acid residue;

A⁹ is an amino acid residue;

20

R¹ is selected from the group: H, F,

C₁-C₆ alkyl substituted with 0-3 R^{1a},

C₂-C₆ alkenyl substituted with 0-3 R^{1a},

C₂-C₆ alkynyl substituted with 0-3 R^{1a}, and

25 C₃-C₆ cycloalkyl substituted with 0-3 R^{1a};

R^{1a} is selected at each occurrence from the group:

Cl, F, Br, I, CF₃, CHF₂, OH, =O, SH,

-CO₂R^{1b}, -SO₂R^{1b}, -SO₃R^{1b}, -P(O)₂R^{1b}, -P(O)₃R^{1b},

30 -C(=O)NHR^{1b}, -NHC(=O)R^{1b}, -SO₂NHR^{1b}, -OR^{1b}, -SR^{1b},

C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy,

-S-(C₁-C₆ alkyl),

aryl substituted with 0-5 R^{1c},

-O-(CH₂)_q-aryl substituted with 0-5 R^{1c},

35 -S-(CH₂)_q-aryl substituted with 0-5 R^{1c}, and

5 5-10 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:
 O, S, and N, and substituted with 0-3 R^{1c};

R^{1b} is H,

10 C₁-C₄ alkyl substituted with 0-3 R^{1c},
 C₂-C₄ alkenyl substituted with 0-3 R^{1c},
 C₂-C₄ alkynyl substituted with 0-3 R^{1c},
 C₃-C₆ cycloalkyl substituted with 0-5 R^{1c},
 C₃-C₆ carbocycle substituted with 0-5 R^{1c},
15 aryl substituted with 0-5 R^{1c}, or
 5-6 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:
 O, S, and N, said heterocyclic group substituted
 with 0-4 R^{1c};

20 R^{1c} is selected at each occurrence from: C₁-C₄ alkyl, Cl,
 F, Br, I, OH, C₁-C₄ alkoxy, -CN, -NO₂, C(O)OR^{1d},
 NR^{1d}R^{1d}, CF₃, and OCF₃;

25 R^{1d} is H or C₁-C₄ alkyl;

R² is H, F, or C₁-C₄ alkyl;

R³ is selected from the group: H,

30 C₁-C₆ alkyl substituted with 0-4 R^{3a},
 C₂-C₆ alkenyl substituted with 0-4 R^{3a},
 C₂-C₆ alkynyl substituted with 0-4 R^{3a},
 -(CH₂)_q- C₃-C₆ cycloalkyl substituted with 0-4 R^{3b},
 -(CH₂)_q-aryl substituted with 0-5 R^{3b}, and
35 -(CH₂)_q-5-10 membered heterocyclic group consisting of
 carbon atoms and 1-4 heteroatoms selected from
 the group: O, S, and N, and said heterocyclic
 group is substituted with 0-2 R^{3b};

5 R^{3a} is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹,
-SR¹¹, -C(=NH)NH₂, and aryl substituted with R^{10b};

R^{3b} is selected from the group: -CO₂H, -NH₂, -OH, -SH, and
-C(=NH)NH₂;

10

R^{3c} is, at each occurrence, independently selected from: H,
C₁-C₆ alkyl, -OH, and OR^{3d};

15

R^{3d} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
-(CH₂)_q- C₃-C₆ cycloalkyl, -(CH₂)_q-aryl, or
-(CH₂)_q-(5-10 membered heterocyclic group), wherein
said heterocyclic group consists of carbon atoms
and 1-4 heteroatoms selected from the group: O,
S, and N;

20

R⁴ is selected from the group: H, C₁-C₆ alkyl, phenyl,
phenylmethyl-, phenylethyl-, C₃-C₆ cycloalkyl,
C₃-C₆ cycloalkylmethyl-, and C₃-C₆ cycloalkylethyl-;

25 R⁵ and R⁷ are independently H or R³;

R⁶ and R⁸ are independently H or R⁴;

30 R⁹ is selected from the group: -S(=O)R^{9a}, -S(=O)₂R^{9a},
-C(=O)R^{9a}, -C(=O)OR^{9a}, -C(=O)NHR^{9a}, C₁-C₃ alkyl-R^{9a},
C₂-C₆ alkenyl-R^{9a}, and C₂-C₆ alkynyl-R^{9a};

R^{9a} is selected from the group:
C₁-C₆ alkyl substituted with 0-3 R^{9b},
35 C₃-C₆ cycloalkyl substituted with 0-3 R^{9c},
aryl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the

5 group: O, S, and N, and said heterocyclic group
is substituted with 0-3 R^{9c};

R^{9b} is selected from the group: phenyl, naphthyl, benzyl,
and 5-10 membered heterocyclic group consisting of
10 carbon atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and R^{9b} is substituted with 0-3
R^{9c};

R^{9c} is selected at each occurrence from the group:
15 CF₃, OCF₃, Cl, F, Br, I, =O, OH, phenyl, C(O)OR¹¹, NH₂,
NH(CH₃), N(CH₃)₂, -CN, NO₂;
C₁-C₄ alkyl substituted with 0-3 R^{9d},
C₁-C₄ alkoxy substituted with 0-3 R^{9d},
C₃-C₆ cycloalkyl substituted with 0-3 R^{9d},
20 aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and said heterocyclic group
is substituted with 0-4 R^{9d};

25 R^{9d} is selected at each occurrence from the group:
C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃, OCF₃, Cl, F, Br, I, =O,
OH, phenyl, C(O)OR¹¹, NH₂, NH(CH₃), N(CH₃)₂, -CN,
and NO₂;

30 n is 1, 2, or 3; and

p is 1 or 2; and

35 q, at each occurrence, is independently 0, 1 or 2.

[10] In a further more preferred embodiment, the present
invention provides novel compounds of Formula IIb, wherein:

5 R¹⁰ is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, and C₁-C₆
alkyl substituted with 0-1 R^{10a};

R^{10a} is selected from the group: halo, -NO₂, -CN, -CF₃,
-CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹, -SR¹¹, -C(=NH)NH₂, and aryl
10 substituted with 0-1 R^{10b};

R^{10b} is selected from the group: -CO₂H, -NH₂, -OH, -SH, and
-C(=NH)NH₂;

15 R^{10c} is H or C₁-C₄ alkyl;

alternatively, R¹⁰ and R^{10c} can be combined to form a C₃-C₆
cycloalkyl group substituted with 0-1 R^{10a};

20 R¹¹ is, at each occurrence, independently H or C₁-C₄ alkyl;

R^{11a} is H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₄ alkenyl,
C₂-C₄ alkynyl, aryl, aryl(C₁-C₄ alkyl)-,
C₃-C₆ cycloalkyl, or C₃-C₆ cycloalkyl(C₁-C₄ alkyl)-;

25

Q¹ is selected from:

-CO₂R¹¹, -SO₂R¹¹, -SO₃R¹¹, -P(O)₂R¹¹, -P(O)₃R¹¹,
aryl substituted with 0-4 Q^{1a}, and

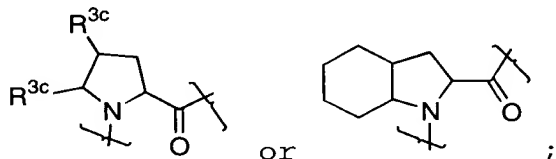
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
O, S, and N, said heterocyclic group substituted
30 with 0-4 Q^{1a};

Q^{1a} is H, F, Cl, Br, I, -NO₂, -CN, -NCS, -CF₃, -OCF₃, -CH₃,
35 -OCH₃, -CO₂R¹⁹, -C(=O)NR¹⁹R¹⁹, -NHC(=O)R¹⁹, -SO₂R¹⁹,
-SO₂NR¹⁹R¹⁹, -NR¹⁹R¹⁹, -OR¹⁹, -SR¹⁹, C₁-C₄ alkyl, C₁-C₄
alkoxy, C₁-C₄ haloalkyl, or C₁-C₄ haloalkoxy;

5 R^{19} is C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, aryl, aryl(C_1 - C_4 alkyl), C_3 - C_6 cycloalkyl, or C_3 - C_6 cycloalkyl(C_1 - C_4 alkyl);

alternatively, $NR^{19}R^{19}$ may form a piperidinyl, piperazinyl,
10 or morpholinyl group;

A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, an amino acid residue,



15 A^3 is a bond or an amino acid residue;

A^4 is a bond or an amino acid residue;

A^5 is a bond;

20

R^1 is selected from the group: H,

C_1 - C_6 alkyl substituted with 0-3 R^{1a} ,

C_2 - C_6 alkenyl substituted with 0-3 R^{1a} ,

C_2 - C_6 alkynyl substituted with 0-3 R^{1a} , and

25 C_3 - C_6 cycloalkyl substituted with 0-3 R^{1a} ;

R^{1a} is selected at each occurrence from the group:

Cl, F, Br, I, CF_3 , CHF_2 , OH, =O, SH,

$-CO_2R^{1b}$, $-SO_2R^{1b}$, $-SO_3R^{1b}$, $-P(O)_2R^{1b}$, $-P(O)_3R^{1b}$,

30 $-C(=O)NHR^{1b}$, $-NHC(=O)R^{1b}$, $-SO_2NHR^{1b}$, $-OR^{1b}$, $-SR^{1b}$,

C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy,

$-S-(C_1-C_6 \text{ alkyl})$,

aryl substituted with 0-5 R^{1c} ,

$-O-(CH_2)_q$ -aryl substituted with 0-5 R^{1c} ,

35 $-S-(CH_2)_q$ -aryl substituted with 0-5 R^{1c} , and

5 5-10 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:
 O, S, and N, and substituted with 0-3 R^{1c} ;

R^{1b} is H,

10 C_1 - C_4 alkyl substituted with 0-3 R^{1c} ,
 C_2 - C_4 alkenyl substituted with 0-3 R^{1c} ,
 C_2 - C_4 alkynyl substituted with 0-3 R^{1c} ,
 C_3 - C_6 cycloalkyl substituted with 0-5 R^{1c} ,
 C_3 - C_6 carbocycle substituted with 0-5 R^{1c} ,
15 aryl substituted with 0-5 R^{1c} , or
 5-6 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the group:
 O, S, and N, said heterocyclic group substituted
 with 0-4 R^{1c} ;

20 R^{1c} is selected at each occurrence from: C_1 - C_4 alkyl, Cl,
 F, Br, I, OH, C_1 - C_4 alkoxy, -CN, -NO₂, C(O)OR^{1d},
 NR^{1d}R^{1d}, CF₃, and OCF₃;

25 R^{1d} is H or C_1 - C_4 alkyl;

R^2 is H or C_1 - C_4 alkyl;

R^3 is selected from the group: H,

30 C_1 - C_6 alkyl substituted with 0-4 R^{3a} ,
 C_2 - C_6 alkenyl substituted with 0-4 R^{3a} ,
 C_2 - C_6 alkynyl substituted with 0-4 R^{3a} ,
 -(CH₂)_q- C_3 - C_6 cycloalkyl substituted with 0-4 R^{3b} ,
 -(CH₂)_q-aryl substituted with 0-5 R^{3b} , and
35 -(CH₂)_q-5-10 membered heterocyclic group consisting of
 carbon atoms and 1-4 heteroatoms selected from
 the group: O, S, and N, and said heterocyclic
 group is substituted with 0-2 R^{3b} ;

5 R^{3a} is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹,
-SR¹¹, -C(=NH)NH₂, and aryl substituted with R^{10b};

R^{3b} is selected from the group: -CO₂H, - NH₂, -OH, -SH, and
-C(=NH)NH₂;

10

R^{3c} is, at each occurrence, independently selected from: H,
C₁-C₆ alkyl, -OH, and OR^{3d};

15

R^{3d} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,
-(CH₂)_q- C₃-C₆ cycloalkyl, -(CH₂)_q-aryl, or
-(CH₂)_q-(5-10 membered heterocyclic group), wherein
said heterocyclic group consists of carbon atoms
and 1-4 heteroatoms selected from the group: O,
S, and N;

20

R⁴ is selected from the group: H, C₁-C₆ alkyl, phenyl,
phenylmethyl-, phenylethyl-, C₃-C₆ cycloalkyl,
C₃-C₆ cycloalkylmethyl-, and C₃-C₆ cycloalkylethyl-;

25

R⁹ is selected from the group: -S(=O)₂R^{9a}, -C(=O)R^{9a},
C₁-C₃ alkyl-R^{9a}, C₂-C₆ alkenyl-R^{9a}, and
C₂-C₆ alkynyl-R^{9a};

30

R^{9a} is selected from the group:
C₁-C₆ alkyl substituted with 0-3 R^{9b},
C₃-C₆ cycloalkyl substituted with 0-3 R^{9c},
aryl substituted with 0-3 R^{9c}, and
5-14 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the
group: O, S, and N, and said heterocyclic group
is substituted with 0-3 R^{9c};

35

R^{9b} is selected from the group: phenyl, naphthyl, benzyl,
and 5-10 membered heterocyclic group consisting of

5 carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and R^{9b} is substituted with 0-3 R^{9c};

R^{9c} is selected at each occurrence from the group:

10 CF₃, OCF₃, Cl, F, Br, I, =O, OH, phenyl, C(O)OR¹¹, NH₂, NH(CH₃), N(CH₃)₂, -CN, NO₂;
C₁-C₄ alkyl substituted with 0-3 R^{9d},
C₁-C₄ alkoxy substituted with 0-3 R^{9d},
C₃-C₆ cycloalkyl substituted with 0-3 R^{9d},
15 aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: O, S, and N, and said heterocyclic group is substituted with 0-4 R^{9d};

20 R^{9d} is selected at each occurrence from the group:

C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃, OCF₃, Cl, F, Br, I, =O, OH, phenyl, C(O)OR¹¹, NH₂, NH(CH₃), N(CH₃)₂, -CN, and NO₂;

25

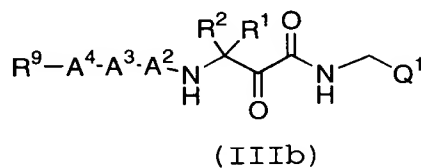
n is 1 or 2; and

p is 1 or 2; and

30 q, at each occurrence, is independently 0, 1 or 2.

[11] In an even more preferred embodiment, the present invention provides novel compounds of Formula IIIb, wherein:

35



5 or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

Q^1 is selected from:

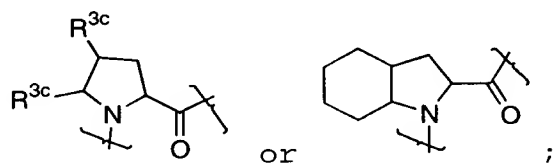
10 $-CO_2R^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$, $-P(O)_2R^{11}$, $-P(O)_3R^{11}$,
aryl substituted with 0-4 Q^{1a} , and
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,
15 pyrazinyl, piperazinyl, piperidinyl, imidazolyl,
imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,
morpholinyl, oxazolyl, oxazolidinyl,
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
thiazolyl, triazinyl, and triazolyl; said
heterocyclic group substituted with 0-4 Q^{1a} ;

20 Q^{1a} is H, F, Cl, Br, I, $-NO_2$, $-CN$, $-NCS$, $-CF_3$, $-OCF_3$, $-CH_3$,
 $-OCH_3$, $-CO_2R^{19}$, $-C(=O)NR^{19}R^{19}$, $-NHC(=O)R^{19}$, $-SO_2R^{19}$,
 $-SO_2NR^{19}R^{19}$, $-NR^{19}R^{19}$, $-OR^{19}$, $-SR^{19}$, C_1-C_4 alkyl, C_1-C_4
alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

25 R^{19} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, aryl, aryl(C_1-C_4
alkyl), C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl(C_1-C_4
alkyl);

30 alternatively, $NR^{19}R^{19}$ may form a piperidinyl, piperazinyl,
or morpholinyl group;

A^2 is a bond, $-NH-CR^3R^4-C(=O)-$, Ala, Arg, Asn, Asp, Aze,
Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu,
35 Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr,
Trp, Tyr, Val,



A^3 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

10

A^4 is a bond, Ala, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, or Val;

15 R^1 is selected from the group: H,

C_1 - C_6 alkyl substituted with 0-3 R^{1a} ,
 C_2 - C_6 alkenyl substituted with 0-3 R^{1a} ,
 C_2 - C_6 alkynyl substituted with 0-3 R^{1a} , and
 C_3 - C_6 cycloalkyl substituted with 0-3 R^{1a} ;

20

R^{1a} is selected at each occurrence from the group:

Cl, F, Br, I, CF_3 , CHF_2 , OH, =O, SH,
 $-CO_2R^{1b}$, $-SO_2R^{1b}$, $-SO_3R^{1b}$, $-P(O)_2R^{1b}$, $-P(O)_3R^{1b}$,
 $-C(=O)NHR^{1b}$, $-NHC(=O)R^{1b}$, $-SO_2NHR^{1b}$, $-OR^{1b}$, $-SR^{1b}$,
 C_1 - C_3 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy,
 $-S-(C_1-C_6 \text{ alkyl})$,

25

aryl substituted with 0-5 R^{1c} ,
 $-O-(CH_2)_q$ -aryl substituted with 0-5 R^{1c} ,
 $-S-(CH_2)_q$ -aryl substituted with 0-5 R^{1c} , and

30

5-10 membered heterocyclic group consisting of carbon atoms and 1-4 heteroatoms selected from the group: pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl,

35

5 1H-indazolyl, benzofuranyl, benzothiofuranyl,
benztetrazolyl, benzotriazolyl, benzisoxazolyl,
benzoxazolyl, oxindolyl, benzoxazoliny, l,
benzthiazolyl, benzisothiazolyl, isatinoyl,
10 isoquinolinyl, octahydroisoquinolinyl,
tetrahydroisoquinolinyl, tetrahydroquinolinyl,
isoxazolopyridinyl, quinazolinyl, quinolinyl,
isothiazolopyridinyl, thiazolopyridinyl,
oxazolopyridinyl, imidazolopyridinyl, and
pyrazolopyridinyl; and substituted with 0-3 R^{1c};

15

R^{1b} is H,

C₁-C₄ alkyl substituted with 0-3 R^{1c},
C₂-C₄ alkenyl substituted with 0-3 R^{1c},
C₂-C₄ alkynyl substituted with 0-3 R^{1c},
20 C₃-C₆ cycloalkyl substituted with 0-5 R^{1c},
C₃-C₆ carbocycle substituted with 0-5 R^{1c},
aryl substituted with 0-5 R^{1c}, or
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the group:
25 pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,
pyrazinyl, piperazinyl, piperidinyl, imidazolyl,
imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,
morpholinyl, oxazolyl, oxazolidinyl,
tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
30 thiazolyl, triazinyl, and triazolyl; said
heterocyclic group substituted with 0-4 R^{1c};

R^{1c} is selected at each occurrence from: C₁-C₄ alkyl, Cl,
F, Br, I, OH, C₁-C₄ alkoxy, -CN, -NO₂, C(O)OR^{1d},
35 NR^{1d}R^{1d}, CF₃, and OCF₃;

R^{1d} is H or C₁-C₄ alkyl;

R² is H or C₁-C₄ alkyl;

40

5 R³ is selected from the group: H,

C₁-C₆ alkyl substituted with 0-4 R^{3a},

C₂-C₆ alkenyl substituted with 0-4 R^{3a},

C₂-C₆ alkynyl substituted with 0-4 R^{3a},

-(CH₂)_q- C₃-C₆ cycloalkyl substituted with 0-4 R^{3b},

10 -(CH₂)_q-aryl substituted with 0-5 R^{3b}, and

-(CH₂)_q-5-10 membered heterocyclic group consisting of

carbon atoms and 1-4 heteroatoms selected from

the group: pyridinyl, furanyl, thienyl, pyrrolyl,

pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,

15 imidazolyl, imidazolidinyl, indolyl, tetrazolyl,

isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,

tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,

thiazolyl, triazinyl, triazolyl, benzimidazolyl,

1H-indazolyl, benzofuranyl, benzothiofuranyl,

20 benztetrazolyl, benzotriazolyl, benzisoxazolyl,

benzoxazolyl, oxindolyl, benzoxazolinyl,

benzthiazolyl, benzisothiazolyl, isatinoyl,

isoquinolinyl, octahydroisoquinolinyl,

tetrahydroisoquinolinyl, tetrahydroquinolinyl,

25 isoxazolopyridinyl, quinazolinyl, quinolinyl,

isothiazolopyridinyl, thiazolopyridinyl,

oxazolopyridinyl, imidazolopyridinyl, and

pyrazolopyridinyl; and said heterocyclic group

is substituted with 0-2 R^{3b};

30

R^{3a} is selected from the group: -CO₂R¹¹, -NR¹¹R¹¹, -OR¹¹,

-SR¹¹, -C(=NH)NH₂, and aryl substituted with R^{10b};

R^{3b} is selected from the group: -CO₂H, -NH₂, -OH, -SH, and

35

-C(=NH)NH₂;

R^{3c} is, at each occurrence, independently selected from: H,

C₁-C₆ alkyl, -OH, and OR^{3d};

40 R^{3d} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,

5 $-(CH_2)_q-$ C₃-C₆ cycloalkyl, $-(CH_2)_q$ -aryl, or
 $-(CH_2)_q$ -(5-10 membered heterocyclic group), wherein
 said heterocyclic group consists of carbon atoms
 and 1-4 heteroatoms selected from the group: O,
 S, and N;

10

R⁴ is selected from the group: H, C₁-C₆ alkyl, phenyl,
phenylmethyl-, phenylethyl-, C₃-C₆ cycloalkyl,
C₃-C₆ cycloalkylmethyl-, and C₃-C₆ cycloalkylethyl-;

15 R⁹ is selected from $-S(=O)_2R^{9a}$ and $-C(=O)R^{9a}$;

R^{9a} is selected from the group:

phenyl substituted with 0-3 R^{9c},
naphthyl substituted with 0-3 R^{9c}, and
20 5-14 membered heterocyclic group consisting of carbon
 atoms and 1-4 heteroatoms selected from the
 group: pyridinyl, furanyl, thienyl, pyrrolyl,
 pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,
 imidazolyl, imidazolidinyl, indolyl, tetrazolyl,
25 isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,
 tetrahydrofuranyl, thiadiazinyl, thiadiazolyl,
 thiazolyl, triazinyl, triazolyl, benzimidazolyl,
 1H-indazolyl, benzofuranyl, benzothiofuranyl,
 benztetrazolyl, benzotriazolyl, benzisoxazolyl,
30 benzoxazolyl, oxindolyl, benzoxazolinyl,
 benzthiazolyl, benzisothiazolyl, isatinoyl,
 isoquinolinyl, octahydroisoquinolinyl,
 tetrahydroisoquinolinyl, tetrahydroquinolinyl,
 isoxazolopyridinyl, quinazolinyl, quinolinyl,
35 isothiazolopyridinyl, thiazolopyridinyl,
 oxazolopyridinyl, imidazolopyridinyl, and
 pyrazolopyridinyl; and said heterocyclic group is
 substituted with 0-3 R^{9c};

40 R^{9c} is selected at each occurrence from the group:

5 CF₃, OCF₃, Cl, F, Br, I, =O, OH, phenyl, C(O)OR¹¹, NH₂,
NH(CH₃), N(CH₃)₂, -CN, NO₂;

C₁-C₄ alkyl substituted with 0-3 R^{9d},
C₁-C₄ alkoxy substituted with 0-3 R^{9d},
C₃-C₆ cycloalkyl substituted with 0-3 R^{9d},
10 aryl substituted with 0-5 R^{9d}, and
5-6 membered heterocyclic group consisting of carbon
atoms and 1-4 heteroatoms selected from the
group: pyridinyl, furanyl, thienyl, pyrrolyl,
pyrazolyl, pyrazinyl, piperazinyl, piperidinyl,
15 imidazolyl, imidazolidinyl, indolyl, tetrazolyl,
isoxazolyl, morpholinyl, oxazolyl, oxazolidinyl,
tetrahydrofuranlyl, thiadiazinyl, thiadiazolyl,
thiazolyl, triazinyl, and triazolyl; and said
heterocyclic group is substituted with 0-4 R^{9d};

20 R^{9d} is selected at each occurrence from the group:

C₁-C₄ alkyl, C₁-C₄ alkoxy, CF₃, OCF₃, Cl, F, Br, I, =O,
OH, phenyl, C(O)OR¹¹, NH₂, NH(CH₃), N(CH₃)₂, -CN,
and NO₂;

25 p is 1 or 2; and

q, at each occurrence, is independently 0, 1 or 2.

30 In another embodiment, the present invention provides
a novel pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a therapeutically
effective amount of a compound of Formula (I), (II), (III),
(IIb), (IIIb) or pharmaceutically acceptable salt form
35 thereof.

In another embodiment, the present invention provides
a novel method of treating HCV infection which comprises
administering to a host in need of such treatment a
40 therapeutically effective amount of a compound of Formula

5 (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides novel compounds of Formula (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt forms thereof for use in therapy.

In another embodiment, the present invention provides the use of novel compounds of Formula (I), (II), (III), (IIb), (IIIb) or pharmaceutically acceptable salt forms thereof for the manufacture of a medicament for the treatment of HCV.

DEFINITIONS

20 The compounds herein described have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Geometric isomers of double bonds such as olefins and C=N double bonds can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention.

30 Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

40 The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that

5 the designated atom's normal valency is not exceeded, and
that the substitution results in a stable compound. When a
substituent is keto (i.e., =O), then 2 hydrogens on the
atom are replaced. Keto substituents are not present on
10 aromatic moieties. When a ring system (e.g., carbocyclic
or heterocyclic) is said to be substituted with a carbonyl
group or a double bond, it is intended that the carbonyl
group or double bond be part (i.e., within) of the ring.

The present invention is intended to include all
isotopes of atoms occurring in the present compounds.
15 Isotopes include those atoms having the same atomic number
but different mass numbers. By way of general example and
without limitation, isotopes of hydrogen include tritium
and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^{1a}) occurs more than one
20 time in any constituent or formula for a compound, its
definition at each occurrence is independent of its
definition at every other occurrence. Thus, for example,
if a group is shown to be substituted with 0-3 R^{1a}, then
said group may optionally be substituted with up to three
25 R^{1a} groups and R^{1a} at each occurrence is selected
independently from the definition of R^{1a}. Also,
combinations of substituents and/or variables are
permissible only if such combinations result in stable
compounds.

30 When a bond to a substituent is shown to cross a bond
connecting two atoms in a ring, then such substituent may
be bonded to any atom on the ring. When a substituent is
listed without indicating the atom via which such
substituent is bonded to the rest of the compound of a
35 given formula, then such substituent may be bonded via any
atom in such substituent. Combinations of substituents
and/or variables are permissible only if such combinations
result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to
40 include both branched and straight-chain saturated
aliphatic hydrocarbon groups having the specified number of

5 carbon atoms. For example, "C₁-C₁₀ alkyl" (or alkylene),
is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉,
and C₁₀ alkyl groups. Additionally, for example, "C₁-C₆
alkyl" denotes alkyl having 1 to 6 carbon atoms. Examples
10 of alkyl include, but are not limited to, methyl, ethyl,
n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl,
n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-
ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

"Alkenyl" or "alkenylene" is intended to include
hydrocarbon chains of either a straight or branched
15 configuration having the specified number of carbon atoms
and one or more unsaturated carbon-carbon bonds which may
occur in any stable point along the chain. For example,
"C₂-C₆ alkenyl" (or alkenylene), is intended to include C₂,
C₃, C₄, C₅, and C₆ alkenyl groups. Examples of alkenyl
20 include, but are not limited to, ethenyl, 1-propenyl, 2-
propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-
pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-
methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

"Alkynyl" or "alkynylene" is intended to include
hydrocarbon chains of either a straight or branched
25 configuration and one or more carbon-carbon triple bonds
which may occur in any stable point along the chain. For
example, "C₂-C₆ alkynyl" (or alkynylene), is intended to
include C₂, C₃, C₄, C₅, and C₆ alkynyl groups; such as
30 ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

"Cycloalkyl" is intended to include saturated ring
groups, having the specified number of carbon atoms. For
example, "C₃-C₆ cycloalkyl" denotes such as cyclopropyl,
cyclobutyl, cyclopentyl, or cyclohexyl.

35 "Alkoxy" or "alkyloxy" represents an alkyl group as
defined above with the indicated number of carbon atoms
attached through an oxygen bridge. For example, "C₁-C₆
alkoxy" (or alkyloxy), is intended to include C₁, C₂, C₃,
C₄, C₅, and C₆ alkoxy groups. Examples of alkoxy include,
40 but are not limited to, methoxy, ethoxy, n-propoxy,
i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and

5 s-pentoxy. Similarly, "alkylthio" or "thioalkoxy" ;
represents an alkyl group as defined above with the
indicated number of carbon atoms attached through a sulphur
bridge.

"Halo" or "halogen" as used herein refers to fluoro,
10 chloro, bromo, and iodo; and "counterion" is used to
represent a small, negatively charged species such as
chloride, bromide, hydroxide, acetate, sulfate, and the
like.

"Haloalkyl" is intended to include both branched and
15 straight-chain saturated aliphatic hydrocarbon groups
having the specified number of carbon atoms, substituted
with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3
and $w = 1$ to $(2v+1)$). Examples of haloalkyl include, but
are not limited to, trifluoromethyl, trichloromethyl,
20 pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl,
heptafluoropropyl, and heptachloropropyl. Examples of
haloalkyl also include "fluoroalkyl" which is intended to
include both branched and straight-chain saturated
aliphatic hydrocarbon groups having the specified number of
25 carbon atoms, substituted with 1 or more fluorine atoms.

As used herein, "carbocycle" is intended to mean any
stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or
7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic,
any of which may be saturated, partially unsaturated, or
30 aromatic. Examples of such carbocycles include, but are
not limited to, cyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,
[3.3.0]bicyclooctane, [4.3.0]bicyclononane,
[4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane,
35 fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or
tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or
"heterocyclic group" is intended to mean a stable 5, 6, or
7- membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12,
40 13, or 14-membered bicyclic heterocyclic ring which is
saturated partially unsaturated or unsaturated (ie.
aromatic or "heteroaryl"), and which consists of carbon

5 atoms and 1, 2, 3 or 4 heteroatoms independently selected
from the group consisting of N, O and S; and including any
bicyclic group in which any of the above-defined
heterocyclic rings is fused to a benzene ring. The
nitrogen and sulfur heteroatoms may optionally be oxidized
10 to -NO-, -SO-, or -SO₂-. The heterocyclic ring may be
attached to its pendant group at any heteroatom or carbon
atom which results in a stable structure. The heterocyclic
rings described herein may be substituted on carbon or on a
nitrogen atom if the resulting compound is stable. If
15 specifically noted, a nitrogen in the heterocycle may
optionally be quaternized. It is preferred that when the
total number of S and O atoms in the heterocycle exceeds 1,
then these heteroatoms are not adjacent to one another. It
is preferred that the total number of S and O atoms in the
20 heterocycle is not more than 1.

Examples of heterocycles include, but are not limited
to, 2-pyrrolidonyl, 2*H*,6*H*-1,5,2-dithiazinyl, 2*H*-pyrrolyl,
3*H*-indolyl, 4-piperidonyl, 4*H*-quinolizinyl,
6*H*-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl,
25 benzofuranyl, benzothiofuranyl, benzothiophenyl,
benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl,
benztetrazolyl, benzisoxazolyl, benzisothiazolyl,
benzimidazalonyl, carbazolyl, 4*aH*-carbazolyl, β -carboliny,
chromanyl, chromenyl, cinnoliny, decahydroquinoliny,
30 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran,
furanyl, furazanyl, imidazolidiny, imidazoliny,
imidazolyl, imidazolopyridiny, 1*H*-indazolyl, indolenyl,
indoliny, indoliziny, indolyl, isatinoyl,
isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny,
35 isoindolyl, isoquinoliny, isothiazolyl,
isothiazolopyridiny, isoxazolyl, isoxazolopyridiny,
morpholiny, naphthyridiny, octahydroisoquinoliny,
oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,
1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny,
40 oxazolyl, oxazolopyridiny, oxazolidiny, perimidiny,
oxindolyl, phenanthridiny, phenanthroliny, phenarsaziny,

5 phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,
phthalazinyl, piperazinyl, piperidinyl, pteridinyl,
piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl,
pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl,
pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole,
10 pyridothiazole, pyridinyl, pyridyl, pyrimidinyl,
pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl,
quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl,
carbolinyl, tetrazolyl, tetrahydrofuranyl,
tetrahydroisoquinolinyl, tetrahydroquinolinyl,
15 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl,
1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl,
thianthrenyl, thiazolyl, thiazolopyridinyl, thienyl,
thienothiazolyl, thienooxazolyl, thienoimidazolyl,
thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl,
20 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

Preferred 5 to 10 membered heterocycles include, but
are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl,
pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl,
imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,
25 morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl,
thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl,
triazolyl, benzimidazolyl, 1H-indazolyl, benzofuranyl,
benzothiofuranyl, benzotetrazolyl, benzotriazolyl,
benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl,
30 benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl,
octahydroisoquinolinyl, tetrahydroisoquinolinyl,
tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl,
quinolinyl, isothiazolopyridinyl, thiazolopyridinyl,
oxazolopyridinyl, imidazolopyridinyl, and
35 pyrazolopyridinyl.

Preferred 5 to 6 membered heterocycles include, but
are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl,
pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl,
imidazolidinyl, indolyl, tetrazolyl, isoxazolyl,
40 morpholinyl, oxazolyl, oxazolidinyl, tetrahydrofuranyl,
thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and

5 triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "aryl", "C₆-C₁₀ aryl" or "aromatic residue", is intended to mean an aromatic moiety containing, if specified, the specified number of carbon
10 atoms. For example, aryl is phenyl, pyridinyl or naphthyl. Unless otherwise specified, "aryl", "C₆-C₁₀ aryl" or "aromatic residue" may be unsubstituted or substituted with 0 to 3 groups selected from H, OH, OCH₃, Cl, F, Br, I, CN, NO₂, NH₂, N(CH₃)H, N(CH₃)₂, CF₃, OCF₃, C(=O)CH₃, SCH₃,
15 S(=O)CH₃, S(=O)₂CH₃, CH₃, CH₂CH₃, CO₂H, and CO₂CH₃.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural
20 amino acids (e.g., L-amino acids), modified and unusual amino acids (e.g., D-amino acids), as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids, such as
25 those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. "Natural amino acids" include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid,
30 glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tyrosine, tyrosine, tryptophan, proline, and valine. Natural non-protein amino acids include, but are not limited to arginosuccinic acid, citrulline, cysteine sulfinic acid,
35 3,4-dihydroxyphenylalanine, homocysteine, homoserine, ornithine, 3-monoiodotyrosine, 3,5-diiodotyrosine, 3,5,5'-triiodothyronine, and 3,3',5,5'-tetraiodothyronine. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to,
40 D-amino acids, hydroxylysine, 4-hydroxyproline, an N-CBZ-protected amino acid, 2,4-diaminobutyric acid,

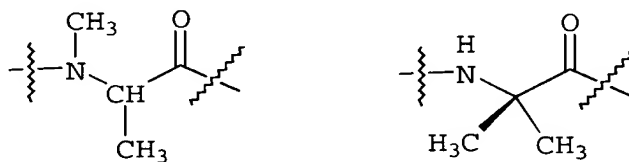
- 5 homoarginine, norleucine, N-methylaminobutyric acid,
naphthylalanine, phenylglycine, β -phenylproline,
tert-leucine, 4-aminocyclohexylalanine,
N-methyl-norleucine, 3,4-dehydroproline,
N,N-dimethylaminoglycine, N-methylaminoglycine,
10 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid,
trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-,
and 4-(aminomethyl)-benzoic acid,
1-aminocyclopentanecarboxylic acid,
1-aminocyclopropanecarboxylic acid, and
15 2-benzyl-5-aminopentanoic acid.

As used throughout the specification, the following
abbreviations for amino acid residues or amino acids apply:

- Abu is L-aminobutyric acid;
20 Ala is L-alanine;
Alg is L-2-amino-4-pentenoic acid;
Ape is L-2-aminopentanoic acid;
Arg is L-arginine;
Asn is L-asparagine;
25 Asp is L-aspartic acid;
Aze is azedine-2-carboxylic acid;
Cha is L-2-amino-3-cyclohexylpropionic acid;
Cpa is L-2-amino-3-cyclopropylpropionic acid
Cpg is L-2-amino-2-cyclopropylacetic acid;
30 Cys is L-cysteine;
Dfb is L-4,4'-difluoro-1-amino-butyric acid;
Dpa is L-2-amino-3,3-diphenylpropionic acid
Gln is L-glutamine;
Glu is L-glutamic acid;
35 Gly is glycine;
His is L-histidine;
HomoLys is L-homolysine;
Hyp is L-4-hydroxyproline;
Ile is L-isoleucine;
40 Irg is isothiuronium analog of L-Arg;
Leu is L-leucine;
Lys is L-lysine;

5 Met is L-methionine;
 Orn is L-ornithine;
 Phe is L-phenylalanine;
 Phe(4-fluoro) is para-fluorophenylalanine;
 Pro is L-proline;
 10 Sar is L-sarcosine;
 Ser is L-serine;
 Thr is L-threonine;
 Tpa is L-2-amino-5,5,5-trifluoropentanoic acid;
 Trp is L-tryptophan;
 15 Tyr is L-tyrosine;
 Val is L-valine; and
 HyPOBn: O-benzyl hydroxylproline.

"Amino acid residue" as used herein, refers to
 20 natural, modified or unnatural amino acids of either D- or
 L-configuration and means an organic compound containing
 both a basic amino group and an acidic carboxyl group.
 Natural amino acids residues are Ala, Arg, Asn, Asp, Aze,
 Cys, Gln, Glu, Gly, His, Hyp, Ile, Irg Leu, Lys, Met, Orn,
 25 Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, and Val.
 Roberts and Vellaccio, The Peptides, Vol 5; 341-449 (1983),
 Academic Press, New York, discloses numerous suitable
 unnatural amino acids and is incorporated herein by
 reference for that purpose. Additionally, said reference
 30 describes, but does not extensively list, acyclic N-alkyl
 and acyclic α,α -disubstituted amino acids. Included in the
 scope of the present invention are N-alkyl, aryl, and
 alkylaryl analogs of both in chain and N-terminal amino
 acid residues. Similarly, alkyl, aryl, and alkylaryl maybe
 35 substituted for the alpha hydrogen. Illustrated below are
 examples of N-alkyl and alpha alkyl amino acid residues,
 respectively.



Unnatural amino acids that fall within the scope of this invention are by way of example and without limitation:

- 2-aminobutanoic acid, 2-aminopentanoic acid, 2-aminohexanoic
 10 acid, 2-aminoheptanoic acid, 2-aminooctanoic acid, 2-aminononanoic acid, 2-aminodecanoic acid, 2-aminoundecanoic acid, 2-amino-3,3-dimethylbutanoic acid, 2-amino-4,4-dimethylpentanoic acid, 2-amino-3-methylhexanoic acid, 2-amino-3-methylheptanoic acid, 2-amino-3-methyloctanoic
 15 acid, 2-amino-3-methylnonanoic acid, 2-amino-4-methylhexanoic acid, 2-amino-3-ethylpentanoic acid, 2-amino-3,4-dimethylpentanoic acid, 2-amino-3,5-dimethylhexanoic acid, 2-amino-3,3-dimethylpentanoic acid, 2-amino-3-ethyl-3-methylpentanoic acid, 2-amino-3,3-diethylpentanoic acid, 2-amino-5-methylhexanoic acid, 2-amino-6-methylheptanoic, 2-amino-7-methyloctanoic, 2-amino-2-cyclopentylacetic, 2-amino-2-cyclohexylacetic acid, 2-amino-2-(1-methylcyclohexyl)acetic acid, 2-amino-2-(2-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(3-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(4-methyl-1-methylcyclohexyl)acetic acid, 2-amino-2-(1-ethylcyclohexyl)acetic acid, 2-amino-3-(cyclohexyl)propanoic acid, 2-amino-4-(cyclohexyl)butanoic acid, 2-amino-3-(1-adamantyl)propanoic acid, 2-amino-3-butenic acid, 2-amino-3-methyl-3-butenic acid, 2-amino-4-pentenoic acid, 2-amino-4-hexenoic acid, 2-amino-5-heptenoic acid, 2-amino-4-methyl-4-hexenoic acid, 2-amino-5-methyl-4-hexenoic acid, 2-amino-4-methyl-5-hexenoic acid, 2-amino-6-heptenoic acid, 2-amino-3,3,4-trimethyl-4-pentenoic acid, 2-amino-4-chloro-4-pentenoic, 2-amino-4,4-dichloro-3-butenic acid, 2-amino-3-(2-methylenecyclopropyl)-propanoic acid, 2-amino-2-(2-cyclopentenyl)acetic acid, 2-amino-2-(cyclohexenyl)acetic acid, 2-amino-3-(2-cyclopentenyl)propanoic acid, 2-amino-3-(3-cyclopentenyl)propanoic acid, 2-amino-3-(1-cyclohexyl)propanoic acid, 2-amino-2-(1-cyclopentenyl)acetic acid, 2-amino-2-(1-cyclohexyl)acetic

- 5 acid, 2-amino-2-(1-cycloheptenyl)acetic acid, 2-amino-2-(1-cyclooctenyl)acetic acid, 2-amino-3-(1-cycloheptenyl)propanoic acid, 2-amino-3-(1,4-cyclohexadienyl)propanoic acid, 2-amino-3-(2,5-cyclohexadienyl)propanoic acid, 2-amino-2-(7-cycloheptatrienyl)acetic acid, 2-amino-4,5-hexadienoic acid, 2-amino-3-butynoic acid, 2-amino-4-pentynoic acid, 2-amino-4-hexynoic acid, 2-amino-4-hepten-6-ynoic acid, 2-amino-3-fluoropropanoic acid, 2-amino-3,3,3-trifluoropropanoic acid, 2-amino-3-fluorobutanoic acid, 2-amino-3-fluoropentanoic acid, 2-amino-3-fluorohexanoic acid, 2-amino-3,3-difluorobutanoic acid, 2-amino-3,3-difluoro-3-phenylpropanoic acid, 2-amino-3-perfluoroethylpropanoic acid, 2-amino-3-perfluoropropylpropanoic acid, 2-amino-3-fluoro-3-methylbutanoic acid, 2-amino-5,5,5-trifluoropentanoic acid, 2-amino-3-methyl-4,4,4-trifluorobutanoic acid, 2-amino-3-trifluoromethyl-4,4,4-trifluorobutanoic acid, 2-amino-3,3,4,4,5,5-heptafluoropentanoic acid, 2-amino-3-methyl-5-fluoropentanoic acid, 2-amino-3-methyl-4-fluoropentanoic acid, 2-amino-5,5-difluorohexanoic acid, 2-amino-4-(fluoromethyl)-5-fluoropentanoic acid, 2-amino-4-trifluoromethyl-5,5,5-trifluoropentanoic acid, 2-amino-3-fluoro-3-methylbutanoic acid, 2-amino-3-fluoro-3-phenylpentanoic acid, 2-amino-2-(1-fluorocyclopentyl)acetic acid, 2-amino-2-(1-fluorocyclohexyl)acetic acid, 2-amino-3-chloropropanoic acid, 2-amino-3-chlorobutanoic acid, 2-amino-4,4-dichlorobutanoic acid, 2-amino-4,4,4-trichlorobutanoic acid, 2-amino-3,4,4-trichlorobutanoic acid, 2-amino-6-chlorohexanoic acid, 2-amino-4-bromobutanoic acid, 2-amino-3-bromobutanoic acid, 2-amino-3-mercaptopentanoic acid, 2-amino-4-mercaptopentanoic acid, 2-amino-3-mercapto-3,3-dimethylpropanoic acid, 2-amino-3-mercapto-3-methylpentanoic acid, 2-amino-3-mercaptopentanoic acid, 2-amino-3-mercapto-4-methylpentanoic acid, 2-amino-3-methyl-4-mercaptopentanoic acid, 2-amino-5-mercapto-5-methylhexanoic acid, 2-amino-2-(1-mercaptopocyclobutyl)acetic acid, 2-amino-2-(1-

- 5 mercaptocyclopentyl)acetic acid, 2-amino-2-(1-mercaptocyclohexyl)acetic acid, 2-amino-5-(methylthio)pentanoic acid, 2-amino-6-(methylthio)hexanoic acid, 2-amino-4-methylthio-3-phenylbutanoic acid, 2-amino-5-ethylthio-5-methylpentanoic acid, 2-amino-5-ethylthio-10 3,5,5-trimethylpentanoic acid, 2-amino-5-ethylthio-5-phenylpentanoic acid, 2-amino-5-ethylthio-5-pentanoic acid, 2-amino-5-butylthio-5-methylpentanoic acid, 2-amino-5-butylthio-3,5,5-trimethylpentanoic acid, 2-amino-5-butylthio-5-phenylpentanoic acid, 2-amino-5-15 (butylthio)pentanoic acid, 2-amino-3-methyl-4-hydroselenopentanoic acid, 2-amino-4-methylselenobutanoic acid, 2-amino-4-ethylselenobutanoic acid, 2-amino-4-benzylselenobutanoic acid, 2-amino-3-methyl-4-(methylseleno)butanoic acid, 2-amino-3-20 (aminomethylseleno)propanoic acid, 2-amino-3-(3-aminopropylseleno)propanoic acid, 2-amino-4-methyltellurobutanoic acid, 2-amino-4-hydroxybutanoic acid, 2-amino-4-hydroxyhexanoic acid, 2-amino-3-hydroxypentanoic acid, 2-amino-3-hydroxyhexanoic acid, 2-amino-3-methyl-4-25 hydroxybutanoic acid, 2-amino-3-hydroxy-3-methylbutanoic acid, 2-amino-6-hydroxyhexanoic acid, 2-amino-4-hydroxyhexanoic acid, 2-amino-3-hydroxy-4-methylpentanoic acid, 2-amino-3-hydroxy-3-methylpentanoic acid, 2-amino-4-hydroxy-3,3-dimethylbutanoic acid, 2-amino-3-hydroxy-4-30 methylpentanoic acid, 2-amino-3-hydroxybutanedioic acid, 2-amino-3-hydroxy-3-phenylpropanoic acid, 2-amino-3-hydroxy-3-(4-nitrophenyl)propanoic acid, 2-amino-3-hydroxy-3-(3-pyridyl)propanoic acid, 2-amino-2-(1-hydroxycyclopropyl)acetic acid, 2-amino-3-(1-35 hydroxycyclohexyl)propanoic acid, 2-amino-3-hydroxy-3-phenylpropanoic acid, 2-amino-3-hydroxy-3-[3-bis(2-chloroethyl)aminophenyl]propanoic acid, 2-amino-3-hydroxy-3-(3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-hydroxy-3-(3,4-methylenedioxyphenyl)propanoic acid, 2-amino-4-fluoro-40 3-hydroxybutanoic acid, 2-amino-4,4,4-trichloro-3-hydroxybutanoic acid, 2-amino-3-hydroxy-4-hexynoic acid, 2-amino-3,4-dihydroxybutanoic acid, 2-amino-3,4,5,6-

5 tetrahydroxyhexanoic acid, 2-amino-4,5-dihydroxy-3-methylpentanoic acid, 2-amino-5,6-dihydroxyhexanoic acid, 2-amino-5-hydroxy-4-(hydroxymethyl)pentanoic acid, 2-amino-4,5-dihydroxy-4-(hydroxymethyl)pentanoic acid, 2-amino-3-hydroxy-5-benzoyloxypentanoic acid, 2-amino-3-(2-aminoethoxy)propanoic acid, 2-amino-4-(2-aminoethoxy)butanoic acid, 2-amino-4-oxobutanoic acid, 2-amino-3-oxobutanoic acid, 2-amino-4-methyl-3-oxopentanoic acid, 2-amino-3-phenyl-3-oxopropanoic acid, 2-amino-4-phenyl-3-oxobutanoic acid, 2-amino-3-methyl-4-oxopentanoic acid, 2-amino-4-oxo-4-(4-hydroxyphenyl)butanoic acid, 2-amino-4-oxo-4-(2-furyl)butanoic acid, 2-amino-4-oxo-4-(2-nitrophenyl)butanoic acid, 2-amino-4-oxo-4-(2-amino-4-chlorophenyl)butanoic acid, 2-amino-3-(4-oxo-1-cyclohexenyl)propanoic acid, 2-amino-3-(4-oxocyclohexenyl)propanoic acid, 2-amino-3-(2,5-dimethyl-3,6-dioxo-1,4-cyclohexadienyl)propanoic acid, 2-amino-3-(1-hydroxy-5-methyl-7-oxo-cyclohepta-1,3,5-trien-2-yl)propanoic acid, 2-amino-3-(1-hydroxy-7-oxo-cyclohepta-1,3,5-trien-3-yl)propanoic acid, 2-amino-3-(1-hydroxy-7-oxo-cyclohepta-1,3,5-trien-4-yl)propanoic acid, 2-amino-4-methoxy-3-butenic acid, 2-amino-4-(2-aminoethoxy)-3-butenic acid, 2-amino-4-(2-amino-3-hydroxypropyl)-3-butenic acid, 2-amino-2-(4-methoxy-1,4-cyclohexadienyl)acetic acid, 2-amino-3,3-diethoxypropanoic acid, 2-amino-4,4-dimethylbutanoic acid, 2-amino-2-(2,3-epoxycyclohexyl)acetic acid, 2-amino-3-(2,3-epoxycyclohexyl)propanoic acid, 2-amino-8-oxo-9,10-epoxydecanoic acid, 2-amino-propanedioic acid, 2-amino-3-methylbutanedioic acid, 2-amino-3,3-dimethylbutanedioic acid, 2-amino-4-methylpentanedioic acid, 2-amino-3-methylpentanedioic acid, 2-amino-3-phenylpentanedioic acid, 2-amino-3-hydroxypentanedioic acid, 2-amino-3-carboxypentanedioic acid, 2-amino-4-ethylpentanedioic acid, 2-amino-4-propylpentanedioic acid, 2-amino-4-isoamylpentanedioic acid, 2-amino-4-phenylpentanedioic acid, 2-amino-hexanedioic acid, 2-amino-heptanedioic acid, 2-amino-decanedioic acid, 2-amino-octanedioic acid, 2-

5 amino-dodecanedioic acid, 2-amino-3-methylenebutanedioic
 acid, 2-amino-4-methylenepentanedioic acid, 2-amino-3-
 fluorobutanedioic acid, 2-amino-4-fluoropentanedioic acid,
 2-amino-3,3-difluorobutanedioic acid, 2-amino-3-
 chloropentanedioic acid, 2-amino-3-hydroxybutanedioic acid,
 10 2-amino-4-hydroxypentanedioic acid, 2-amino-4-
 hydroxyhexanedioic acid, 2-amino-3,4-dihydroxypentanedioic
 acid, 2-amino-3-(3-hydroxypropyl)butanedioic acid, 2-amino-
 3-(1-carboxy-4-hydroxy-2-cyclodienyl)propanoic acid, 2-
 amino-3-(aceto)butanedioic acid, 2-amino-3-cyanobutanedioic
 15 acid, 2-amino-3-(2-carboxy-6-oxo-6H-pyranyl)propanoic acid,
 2-amino-3-carboxybutanedioic acid, 2-amino-4-
 carboxypentanedioic acid, 3-amido-2-amino-3-
 hydroxypropanoic acid, 3-amido-2-amino-3-methylpropanoic
 acid, 3-amido-2-amino-3-phenylpropanoic acid, 3-amido-2,3-
 20 diaminopropanoic acid, 3-amido-2-amino-3-[N-(4-
 hydroxyphenyl)amino]propanoic acid, 2,3-diaminopropanoic
 acid, 2,3-diaminobutanoic acid, 2,4-diaminobutanoic acid,
 2,4-diamino-3-methylbutanoic acid, 2,4-diamino-3-
 phenylbutanoic acid, 2-amino-3-(methylamino)butanoic acid,
 25 2,5-diamino-3-methylpentanoic acid, 2,7-diaminoheptanoic
 acid, 2,4-diaminoheptanoic acid, 2-amino-2-(2-
 piperidyl)acetic acid, 2-amino-2-(1-aminocyclohexyl)acetic
 acid, 2,3-diamino-3-phenylpropanoic acid, 2,3-diamino-3-(4-
 hydroxyphenyl)propanoic acid, 2,3-diamino-3-(4-
 30 methoxyphenyl)propanoic acid, 2,3-diamino-3-[4-(N,N'-
 dimethylamino)phenyl]propanoic acid, 2,3-diamino-3-(3,4-
 dimethoxyphenyl)propanoic acid, 2,3-diamino-3-(3,4-
 methylenedioxyphenyl)propanoic acid, 2,3-diamino-3-(4-
 hydroxy-3-methoxyphenyl)propanoic acid, 2,3-diamino-3-(2-
 35 phenylethyl)propanoic acid, 2,3-diamino-3-propylpropanoic
 acid, 2,6-diamino-4-hexenoic acid, 2,5-diamino-4-
 fluoropentanoic acid, 2,6-diamino-5-fluorohexanoic acid,
 2,6-diamino-4-hexynoic acid, 2,6-diamino-5,5-
 difluorohexanoic acid, 2,6-diamino-5,5-dimethylhexanoic
 40 acid, 2,5-diamino-3-hydroxypentanoic acid, 2,6-diamino-3-
 hydroxyhexanoic acid, 2,5-diamino-4-hydroxypentanoic acid,
 2,6-diamino-4-hydroxyhexanoic acid, 2,6-diamino-4-

- 5 oxohexanoic acid, 2,7-diaminooctanedioic acid, 2,6-diamino-3-carboxyhexanoic acid, 2,5-diamino-4-carboxypentanoic acid, 2-amino-4-(2-(N,N'-diethylamino)ethyl)pentandioic acid, 2-amino-4-(N,N'-diethylamino)pentandioic acid, 2-amino-4-(N-morpholino)pentandioic acid, 2-amino-4-(N,N'-bis(2-chloroethyl)amino)pentandioic acid, 2-amino-4-(N,N'-bis(2-hydroxyethyl)amino)pentandioic acid, 2,3,5-triaminopentanoic acid, 2-amino-3-(N-(2-aminethyl)amino)propanoic acid, 2-amino-3-((2-aminoethyl)seleno)propanoic acid, 2-amino-3-[(2-aminoethyl)thio]propanoic acid, 2-amino-4-aminooxybutanoic acid, 2-amino-5-hydroxyaminopentanoic acid, 2-amino-5-[N-(5-nitro-2-pyrimidinyl)amino]pentanoic acid, 2-amino-4-[(7-nitro-2,1,3-benzoxadiazol-4-yl)amino]butanoic acid, 2-amino-3-guanidinopropanoic acid, 2-amino-3-guanidinobutanoic acid, 2-amino-4-guanidobutanoic acid, 2-amino-6-guanidohexanoic acid, 2-amino-6-ureidohexanoic acid, 2-amino-3-(2-iminoimidiazolin-4-yl)propanoic acid, 2-amino-2-(2-iminohexahydropyrimidin-4-yl)acetic acid, 2-amino-3-(2-iminohexahydropyrimidin-4-yl)propanoic acid, 2-amino-4-fluoro-5-guanidopentanoic acid, 2-amino-4-hydroxy-5-guanidopentanoic acid, 2-amino-4-guanidooxybutanoic acid, 2-amino-6-amidinohexanoic acid, 2-amino-5-(N-acetimidoylamino)pentanoic acid, 1-aminocyclopropanecarboxylic acid, 1-amino-4-ethylcyclopropanecarboxylic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopentanecarboxylic acid, 1-amino-2,2,5,5-tetramethyl-cyclohexanecarboxylic acid, 1-aminocycloheptanecarboxylic acid, 1-aminocyclononanecarboxylic acid, 2-aminoindan-2-carboxylic acid, 2-aminonorbornane-2-carboxylic acid, 2-amino-3-phenylnorbornane-2-carboxylic acid, 3-aminotetrahydrothiophene-3-carboxylic acid, 1-amino-1,3-cyclohexanedicarboxylic acid, 3-aminopyrrolidine-3-carboxylic acid, 1,4-diaminocyclohexanecarboxylic acid, 6-alkoxy-3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acid, 2-aminobenzobicyclo[2,2,2]octane-2-carboxylic acid,

- 5 2-aminoindan-2-carboxylic acid, 1-amino-2-(3,4-dihydroxyphenyl)cyclopropanecarboxylic acid, 5,6-dialkoxy-2-aminoindane-2-carboxylic acid, 4,5-dihydroxy-2-aminoindan-2-carboxylic acid, 5,6-dihydroxy-2-aminotetralin-2-carboxylic acid, 2-amino-2-cyanoacetic acid, 2-amino-3-cyanopropanoic acid, 2-amino-4-cyanobutanoic acid, 2-amino-5-nitropentanoic acid, 2-amino-6-nitrohexanoic acid, 2-amino-4-aminooxybutanoic acid, 2-amino-3-(N-nitrosohydroxyamino)propanoic acid, 2-amino-3-ureidopropanoic acid, 2-amino-4-ureidobutanoic acid, 2-amino-3-phosphopropanoic acid, 2-amino-3-thiophosphopropanoic acid, 2-amino-4-methanephosphonylbutanoic acid, 2-amino-3-(trimethylsilyl)propanoic acid, 2-amino-3-(dimethyl(trimethylsilylmethylsilyl)propanoic acid, 2-amino-2-phenylacetic acid, 2-amino-2-(3-chlorophenyl)acetic acid, 2-amino-2-(4-chlorophenyl)acetic acid, 2-amino-2-(3-fluorophenyl)acetic acid, 2-amino-2-(3-methylphenyl)acetic acid, 2-amino-2-(4-fluorophenyl)acetic acid, 2-amino-2-(4-methylphenyl)acetic acid, 2-amino-2-(4-methoxyphenyl)acetic acid, 2-amino-2-(2-fluorophenyl)acetic acid, 2-amino-2-(2-methylphenyl)acetic acid, 2-amino-2-(4-chloromethylphenyl)acetic acid, 2-amino-2-(4-hydroxymethylphenyl)acetic acid, 2-amino-2-[4-(methylthiomethyl)phenyl]acetic acid, 2-amino-2-(4-bromomethylphenyl)acetic acid, 2-amino-2-(4-(methoxymethyl)phenyl)acetic acid, 2-amino-2-(4-((N-benzylamino)methyl)phenyl)acetic acid, 2-amino-2-(4-hydroxyphenyl)acetic acid, 2-amino-2-(3-hydroxyphenyl)acetic acid, 2-amino-2-(3-carboxyphenyl)acetic acid, 2-amino-2-(4-aminophenyl)acetic acid, 2-amino-2-(4-azidophenyl)acetic acid, 2-amino-2-(3-t-butyl-4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-difluoro-4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-dihydroxyphenyl)acetic acid, 2-amino-2-(3-carboxy-4-hydroxyphenyl)acetic acid, 2-amino-2-(3,5-di-t-butyl-4-hydroxyphenyl)acetic acid, 2-amino-3-(2-methylphenyl)propanoic acid, 2-amino-3-(4-

- 5 ethylphenyl)propanoic acid, 2-amino-3-(4-
phenylphenyl)propanoic acid, 2-amino-3-(4-
benzylphenyl)propanoic acid, 2-amino-3-(3-
fluorophenyl)propanoic acid, 2-amino-3-(4-
methylphenyl)propanoic acid, 2-amino-3-(4-
10 fluorophenyl)propanoic acid, 2-amino-3-(4-
chlorophenyl)propanoic acid, 2-amino-3-(2-
chlorophenyl)propanoic acid, 2-amino-3-(4-
bromophenyl)propanoic acid, 2-amino-3-(2-
bromophenyl)propanoic acid, 2-amino-3-(3-
15 hydroxyphenyl)propanoic acid, 2-amino-3-(2-
hydroxyphenyl)propanoic acid, 2-amino-3-(4-
mercaptophenyl)propanoic acid, 2-amino-3-(3-
trifluoromethylphenyl)propanoic acid, 2-amino-3-(3-
hydroxyphenyl)propanoic acid, 2-amino-3-(4-
20 hydroxyphenyl)propanoic acid, 2-amino-3-[4-
(hydroxymethyl)phenyl]propanoic acid, 2-amino-3-[3-
(hydroxymethyl)phenyl]propanoic acid, 2-amino-3-[3-
(aminomethyl)phenyl]propanoic acid, 2-amino-3-(3-
carboxyphenyl)propanoic acid, 2-amino-3-(4-
25 nitrophenyl)propanoic acid, 2-amino-3-(4-
aminophenyl)propanoic acid, 2-amino-3-(4-
azidophenyl)propanoic acid, 2-amino-3-(4-
cyanophenyl)propanoic acid, 2-amino-3-(4-
acetophenyl)propanoic acid, 2-amino-3-(4-
30 guanidinophenyl)propanoic acid, 2-amino-3-[4-
(phenylazo)phenyl]propanoic acid, 2-amino-3-[4-(2-
phenylethylenyl)phenyl]propanoic acid, 2-amino-3-(4-
trialkylsilylphenyl)propanoic acid, 2-amino-3-(2,4-
dimethylphenyl)propanoic acid, 2-amino-3-(2,3-
35 dimethylphenyl)propanoic acid, 2-amino-3-(2,5-
dimethylphenyl)propanoic acid, 2-amino-3-(3,5-
dimethylphenyl)propanoic acid, 2-amino-3-(2,4,6-
trimethylphenyl)propanoic acid, 2-amino-3-(3,4,5-
trimethylphenyl)propanoic acid, 2-amino-3-(2,3,4,5,6-
40 pentamethylphenyl)propanoic acid, 2-amino-3-(2,4,-
difluorophenyl)propanoic acid, 2-amino-3-(3,4,-
difluorophenyl)propanoic acid, 2-amino-3-(2,5,-

- 5 difluorophenyl)propanoic acid, 2-amino-3-(2,6,-
difluorophenyl)propanoic acid, 2-amino-3-(2,3,5,6-
tetrafluorophenyl)propanoic acid, 2-amino-3-(3,5-dichloro-
2,4,6-trifluorophenyl)propanoic acid, 2-amino-3-(2,3-
difluorophenyl)propanoic acid, 2-amino-3-(2,3-
- 10 bistrifluoromethylphenyl)propanoic acid, 2-amino-3-(2,4-
bistrifluoromethylphenyl)propanoic acid, 2-amino-3-(2-
chloro-5-trifluoromethylphenyl)propanoic acid, 2-amino-3-
(2,5-difluorophenyl)propanoic acid, 2-amino-3-(2,3,4,5,6-
pentafluorophenyl)propanoic acid, 2-amino-3-(2,3-
- 15 dibromophenyl)propanoic acid, 2-amino-3-(2,5-
dibromophenyl)propanoic acid, 2-amino-3-(3,4-
dibromophenyl)propanoic acid, 2-amino-3-(3,4,5-
triiodophenyl)propanoic acid, 2-amino-3-(2,3-
dihydroxyphenyl)propanoic acid, 2-amino-3-(2,5-
- 20 dihydroxyphenyl)propanoic acid, 2-amino-3-(2,6-
dihydroxyphenyl)propanoic acid, 2-amino-3-(3-bromo-5-
methoxyphenyl)propanoic acid, 2-amino-3-(2,5-
dimethoxyphenyl)propanoic acid, 2-amino-3-(2,5-dimethoxy-4-
methylphenyl)propanoic acid, 2-amino-3-(4-bromo-2,5-
- 25 dimethoxyphenyl)propanoic acid, 2-amino-3-(3-carboxy-4-
hydroxyphenyl)propanoic acid, 2-amino-3-(3-carboxy-4-
aminophenyl)propanoic acid, 2-amino-3-(2-hydroxy-5-
nitrophenyl)propanoic acid, 2-amino-3-(2-ethoxy-5-
nitrophenyl)propanoic acid, 2-amino-3-(3,4,5-
- 30 trimethoxyphenyl)propanoic acid, 2-amino-3-(4-azido-2-
nitrophenyl)propanoic acid, 2-amino-3-(2-hydroxy-5-
nitrophenyl)propanoic acid, 2-amino-3-(2,4-bis-
trimethylsilylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-
3,5-di-t-butylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-
- 35 3-benzylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-
fluorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-2,3,5,6-
tetrafluorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-
dichlorophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-
iodophenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-
- 40 diiodophenyl)propanoic acid, 2-amino-3-(4-hydroxy-2-
hydroxyphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-
hydroxymethylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-2-

- 5 hydroxy-6-methylphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3-carboxyphenyl)propanoic acid, 2-amino-3-(4-hydroxy-3,5-dinitrophenyl)propanoic acid, substituted thyronines, 2-amino-3-(3,4-dihydroxy-2-chlorophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-bromophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-fluorophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-nitrophenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-methylphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-ethylphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-2-isopropylphenyl)propanoic acid, 2-amino-3-(2-t-butyl-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(3-fluoro-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(2-fluoro-4,5-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,5,6-trifluoro-3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,6-dibromo-3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(5,6-dibromo-3,4-dihydroxyphenyl)propanoic acid, 2-amino-3-(2,4,5-trihydroxyphenyl)propanoic acid, 2-amino-3-(2,3,4-trihydroxyphenyl)propanoic acid, 2-amino-3-(3,4-dihydroxy-5-methoxyphenyl)propanoic acid, 2-amino-3-methyl-3-phenylpropanoic acid, 2-amino-3-ethyl-3-phenylpropanoic acid, 2-amino-3-isopropyl-3-phenylpropanoic acid, 2-amino-3-butyl-3-phenylpropanoic acid, 2-amino-3-benzyl-3-phenylpropanoic acid, 2-amino-3-phenylethyl-3-phenylpropanoic acid, 2-amino-3-(4-chlorophenyl)-3-phenylpropanoic acid, 2-amino-3-(4-methoxyphenyl)-3-phenylpropanoic acid, 2-amino-3,3-diphenylpropanoic acid, 2-amino-3-[4-(N,N-diethylamino)phenyl]heptanoic acid, 2-amino-3-[4-(N,N-diethylamino)phenyl]pentanoic acid, 2-amino-3-(3,4-dimethoxyphenyl)pentanoic acid, 2-amino-3-(3,4-dihydroxyphenyl)pentanoic acid, 2-amino-3-methyl-3-phenylbutanoic acid, 2-amino-3-ethyl-3-phenylpentanoic acid, 2-amino-3-methyl-3-phenylpentanoic acid, 2-amino-3,3-diphenylbutanoic acid, 2-amino-3-fluoro-3-phenylpropanoic acid, 2-amino-3-methylene-3-phenylpropanoic acid, 2-amino-3-methylmercapto-3-phenylpropanoic acid, 2-amino-4-methylmercapto-4-phenylbutanoic acid, 2-amino-4-(3,4-dihydroxyphenyl)butanoic acid, 2-amino-5-(4-

5 methoxyphenyl)pentanoic acid, 2-amino-4-phenylbutanoic
 acid, 2-amino-5-phenylpentanoic acid, 2-amino-3,3-dimethyl-
 5-phenylpentanoic acid, 2-amino-4-phenyl-3-butenic acid,
 2-amino-4-phenoxybutanoic acid, 2-amino-5-phenoxy-pentanoic
 acid, 2-amino-2-(indanyl)acetic acid, 2-amino-2-(1-
 10 tetralyl)acetic acid, 2-amino-4,4-diphenylbutanoic acid, 2-
 amino-2-(2-naphthyl)acetic acid, 2-amino-3-(1-
 naphthyl)propanoic acid, 2-amino-3-(1-naphthyl)pentanoic
 acid, 2-amino-3-(2-naphthyl)propanoic acid, 2-amino-3-(1-
 chloro-2-naphthyl)propanoic acid, 2-amino-3-(1-bromo-2-
 15 naphthyl)propanoic acid, 2-amino-3-(4-hydroxy-1-
 naphthyl)propanoic acid, 2-amino-3-(4-methoxy-1-
 naphthyl)propanoic acid, 2-amino-3-(4-hydroxy-2-chloro-1-
 naphthyl)propanoic acid, 2-amino-3-(2-chloro-4-methoxy-1-
 naphthyl)propanoic acid, 2-amino-2-(2-anthryl)acetic acid,
 20 2-amino-3-(9-anthryl)propanoic acid, 2-amino-3-(2-
 fluorenyl)propanoic acid, 2-amino-3-(4-fluorenyl)propanoic
 acid, 2-amino-3-(carboranyl)propanoic acid, 3-
 methylproline, 4-methylproline, 5-methylproline, 4,4-
 dimethylproline, 4-fluoroproline, 4,4-difluoroproline, 4-
 25 bromoproline, 4-chloroproline, 4-aminoproline, 3,4-
 dehydroproline, 4-methylproline, 4-methyleneproline, 4-
 mercaptoproline, 4-(4-methoxybenzylmercapto)proline, 4-
 hydroxymethylproline, 3-hydroxyproline, 3-hydroxy-5-
 methylproline, 3,4-dihydroxyproline, 3-phenoxyproline, 2-
 30 aminoproline, 5-aminoproline, 3-carbamylalkylproline, 4-
 cyano-5-methyl-5-carboxyproline, 4,5-dicarboxyl-5-
 methylproline, 2-aziridinecarboxylic acid, 2-
 azetidinedicarboxylic acid, 4-methyl-2-azetidinedicarboxylic
 acid, pipecolic acid, 1,2,3,6-tetrahydropicolinic acid,
 35 3,4-methyleneproline, 2,4-methyleneproline, 4-
 aminopipecolic acid, 5-hydroxypipecolic acid, 4,5-
 dihydroxypipecolic acid, 5,6-dihydroxy-2,3-dihydroindole-2-
 carboxylic acid, 1,2,3,4-tetrahydroquinoline-2-carboxylic
 acid, 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-
 40 carboxylic acid, 6-hydroxy-1-methyl-1,2,3,4-
 tetrahydroisoquinoline-3-carboxylic acid, 6,7-dihydroxy-1-
 methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

- 5 1,3-oxazolidine-4-carboxylic acid, 1,2-oxazolidine-3-carboxylic acid, perhydro-1,4-thiazine-3-carboxylic acid, 2,2-dimethylthiazolidine-4-carboxylic acid, perhydro-1,3-thiazine-2-carboxylic acid, selenazolidine-4-carboxylic acid, 2-phenylthiazolidine-4-carboxylic acid, 2-(4-carboxylicyl)thiazolidine-4-carboxylic acid, 1,2,3,4,4a,9a-hexahydro-beta-carboline-3-carboxylic acid, 2,3,3a,8a-tetrahydropyrrolo(2,3b)indole-2-carboxylic acid, 2-amino-3-(2-pyridyl)propanoic acid, 2-amino-3-(3-pyridyl)propanoic acid, 2-amino-3-(4-pyridyl)propanoic acid, 2-amino-3-(2-bromo-3-pyridyl)propanoic acid, 2-amino-3-(2-bromo-4-pyridyl)propanoic acid, 2-amino-3-(2-bromo-5-pyridyl)propanoic acid, 2-amino-3-(2-bromo-6-pyridyl)propanoic acid, 2-amino-3-(2-chloro-3-pyridyl)propanoic acid, 2-amino-3-(2-chloro-4-pyridyl)propanoic acid, 2-amino-3-(2-chloro-5-pyridyl)propanoic acid, 2-amino-3-(2-chloro-6-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-3-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-4-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-5-pyridyl)propanoic acid, 2-amino-3-(2-fluoro-6-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-3-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-4-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-5-pyridyl)propanoic acid, 2-amino-3-(1,2-dihydro-2-oxo-6-pyridyl)propanoic acid, 2-amino-3-(5-hydroxy-2-pyridyl)propanoic acid, 2-amino-3-(5-hydroxy-6-iodo-2-pyridyl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxo-1,4-dihydro-1-pyridyl)propanoic acid, N-(5-carboxyl-5-aminopentyl)pyridinium chloride, 1,2,5-trimethyl-4-(2-amino-2-carboxy-1-hydroxyethyl)pyridinium chloride, 2-amino-2-(5-chloro-2-pyridyl)acetic acid, N-(3-amino-3-carboxypropyl)pyridinium chloride, 2-amino-3-(2-pyrryl)propanoic acid, 2-amino-3-(1-pyrryl)propanoic acid, 2-amino-4-(1-pyrryl)butanoic acid, 2-amino-5-(1-pyrryl)pentanoic acid, 2-amino-3-(5-imidazolyl)-3-methylpropanoic acid, 2-amino-3-(5-imidazolyl)-3-ethylpropanoic acid, 2-amino-3-hexyl-3-(5-

- 5 imidazolyl)propanoic acid, 2-amino-3-hydroxy-3-(5-imidazolyl)propanoic acid, 2-amino-3-(4-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(4-methyl-5-imidazolyl)propanoic acid, 2-amino-3-(2-methyl-5-imidazolyl)propanoic acid, 2-amino-3-(4-fluoro-5-imidazolyl)propanoic acid, 2-amino-3-(2-fluoro-5-imidazolyl)propanoic acid, 2-amino-3-(2-amino-5-imidazolyl)propanoic acid, 2-amino-3-(2-phenylaza-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-2-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-4-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(1-methyl-5-nitro-5-imidazolyl)propanoic acid, 2-amino-3-(2-mercapto-5-imidazolyl)propanoic acid, 2-amino-4-(5-imidazolyl)butanoic acid, 2-amino-3-(1-imidazolyl)propanoic acid, 2-amino-3-(2-imidazolyl)propanoic acid, 2-amino-(1-pyrazolyl)propanoic acid, 2-amino-(3-pyrazolyl)propanoic acid, 2-amino-(3,5-dialkyl-4-pyrazolyl)propanoic acid, 2-amino-3-(3-amino-1,2,4-triazol-1-yl)propanoic acid, 2-amino-3-(tetrazol-5-yl)propanoic acid, 2-amino-4-(5-tetrazolyl)butanoic acid, 2-amino-3-(6-methyl-3-indolyl)propanoic acid, 2-amino-3-(4-fluoro-3-indolyl)propanoic acid, 2-amino-3-(5-fluoro-3-indolyl)propanoic acid, 2-amino-3-(6-fluoro-3-indolyl)propanoic acid, 2-amino-3-(4,5,6,7-tetrafluoro-3-indolyl)propanoic acid, 2-amino-3-(5-chloro-3-indolyl)propanoic acid, 2-amino-3-(6-chloro-3-indolyl)propanoic acid, 2-amino-3-(7-chloro-3-indolyl)propanoic acid, 2-amino-3-(5-bromo-3-indolyl)propanoic acid, 2-amino-3-(7-bromo-3-indolyl)propanoic acid, 2-amino-3-(2-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(5-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(7-hydroxy-3-indolyl)propanoic acid, 2-amino-3-(2-alkylmercapto-3-indolyl)propanoic acid, 2-amino-3-(7-amino-3-indolyl)propanoic acid, 2-amino-3-(4-nitro-3-indolyl)propanoic acid, 2-amino-3-(7-nitro-3-indolyl)propanoic acid, 2-amino-3-(4-carboxy-3-indolyl)propanoic acid, 2-amino-3-(3-indolyl)butanoic acid, 2-amino-3-(2,3-dihydro-3-indolyl)propanoic acid, 2-amino-3-

- 5 (2,3-dihydro-2-oxo-3-indolyl)propanoic acid, 2-amino-3-alkylmercapto-3-(3-indolyl)propanoic acid, 2-amino-3-(4-aza-3-indolyl)propanoic acid, 2-amino-3-(7-aza-3-indolyl)propanoic acid, 2-amino-3-(7-aza-6-chloro-4-methyl-3-indolyl)propanoic acid, 2-amino-3-(2,3-dihydrobenzofuran-3-yl)propanoic acid, 2-amino-3-(3-methyl-5-7-dialkylbenzofuran-2-yl)propanoic acid, 2-amino-3-(benzothiophen-3-yl)propanoic acid, 2-amino-3-(5-hydroxybenzothiophen-3-yl)propanoic acid, 2-amino-3-eoenzoselenol-3yl)propanoic acid, 2-amino-3-quinolylpropanoic acid, 2-amino-3-(8-hydroxy-5-quinolyl)propanoic acid, 2-amino-2-(5,6,7,8-tetrahydroquinol-5-yl)acetic acid, 2-amino-3-(3-coumarinyl)propanoic acid, 2-amino-2-(benzisoxazol-3-yl)acetic acid, 2-amino-2-(5-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(6-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(7-methylbenzisoxazol-3-yl)acetic acid, 2-amino-2-(5-bromobenzisoxazol-3-yl)acetic acid, 2-amino-3-(benzimidazol-2-yl)propanoic acid, 2-amino-3-(5,6-dichlorobenzimidazol-2-yl)propanoic acid, 2-amino-3-(5,6-dimethylbenzimidazol-2-yl)propanoic acid, 2-amino-3-(4,5,6,7-hydrobenzirnidazol-2-yl)propanoic acid, 2-amino-2-(benzimidazol-5-yl)acetic acid, 2-amino-2-(1,3-dihydro-2,2-dioxoisobenzothiophen-5-yl)acetic acid, 2-amino-2-(1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl)acetic acid, 2-amino-2-(2-oxobenzimidazol-5-yl)acetic acid, 2-amino-3-(4-hydroxybenzothiazol-6-yl)propanoic acid, 2-amino-3-(benzoxazol-2-yl)propanoic acid, 2-amino-3-(benzothiazol-2-yl)propanoic acid, 2-amino-3-(9-adeninyl)propanoic acid, 2-amino-2-(6-chloro-9-purinyl)acetic acid, 2-amino-2-(6-amino-9-purinyl)acetic acid, 2-amino-3-(6-purinyl)propanoic acid, 2-amino-3-(8-theobrominyl)propanoic acid, 2-amino-2-(1-uracilyl)acetic acid, 2-amino-2-(1-cytosinyl)acetic acid, 2-amino-3-(1-uracilyl)propanoic acid, 2-amino-3-(1-cytosinyl)propanoic acid, 2-amino-4-(1-pyrimidinyl)butanoic acid, 2-amino-4-(4-amino-1-pyrimidinyl)butanoic acid, 2-amino-4-(4-hydroxy-1-pyrimidinyl)butanoic acid, 2-amino-5-(1-pyrimidinyl)pentanoic acid, 2-amino-5-(4-amino-1-

5 pyrimidinyl)pentanoic acid, 2-amino-5-(4-hydroxy-1-
 pyrimidinyl)pentanoic acid, 2-amino-3-(5-
 pyrimidinyl)propanoic acid, 2-amino-3-(6-uracilyl)propanoic
 acid, 2-amino-3-(2-pyrimidinyl)propanoic acid, 2-amino-3-
 (6-amino-4-chloro-2-pyrimidinyl)propanoic acid, 2-amino-3-
 10 (4-hydroxy-2-pyrimidinyl)propanoic acid, 2-amino-3-(2-
 amino-4-pyrimidinyl)propanoic acid, 2-amino-3-(4,5-
 dihydroxypyrimidin-2-yl)propanoic acid, 2-amino-3-(2-
 thiouracil-6-yl)propanoic acid, 2-amino-2-(5-alkyl-2-
 tetrahydrofuryl)acetic acid, 2-amino-2-(5-methyl-2,5-
 15 dihydro-2-furyl)acetic acid, 2-amino-2-(5-alkyl-2-
 furyl)acetic acid, 2-amino-2-(2-furyl)acetic acid, 2-amino-
 2-(3-hydroxy-5-methyl-4-isoxazolyl)acetic acid, 2-amino-3-
 (4-bromo-3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-3-
 (4-methyl-3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-3-
 20 (3-hydroxy-5-isoxazolyl)propanoic acid, 2-amino-2-(3-
 chloro-D2 -isoxazolin-5-yl)acetic acid, 2-amino-2-(3-oxo-5-
 isoxazolidinyl)acetic acid, 2-amino-3-(3,5-dioxo-1,2,4-
 oxadiazolin-2-yl)propanoic acid, 2-amino-3-(3-phenyl-5-
 isoxazolyl)propanoic acid, 2-amino-3-[3-(4-hydroxyphenyl)-
 25 1,2,4-oxadiazol-5-yl]propanoic acid, 2-amino-3-(2-
 thienyl)propanoic acid, 2-amino-2-(2-furyl)acetic acid, 2-
 amino-2-(2-thienyl)acetic acid, 2-amino-2-(2-
 thiazolyl)acetic acid, 2-amino-3-(2-thiazolyl)propanoic
 acid, 2-amino-4-(4-carboxy-2-thiazolyl)butanoic acid, 2-
 30 amino-3-(4-thiazolyl)propanoic acid, 2-amino-3-(2-
 selenolyl)propanoic acid, 2-amino-3-(2-amino-4-
 selenolyl)propanoic acid, and
 2-amino-3-(beta-ribofuranosyl)propanoic acid.

"Amino acids residue" also refers to various amino
 35 acids where sidechain functional groups are coupled with
 appropriate protecting groups known to those skilled in the
 art. "The Peptides", Vol 3, 3-88 (1981)discloses numerous
 suitable protecting groups and is incorporated herein by
 reference for that purpose. Examples of amino acids where
 40 sidechain functional groups are coupled with appropriate
 protecting groups include, but are not limited to,
 Asp(OMe), Glu(OMe), Hyp(OMe), Asp(O^tBu), Glu(O^tBu),

5 Hyp(O^tBu), Thr(O^tBu), Asp(OBzl), Glu(OBzl), Hyp(OBzl), and
Thr(OBzl).

The phrase "pharmaceutically acceptable" is employed
herein to refer to those compounds, materials,
10 compositions, and/or dosage forms which are, within the
scope of sound medical judgment, suitable for use in
contact with the tissues of human beings and animals
without excessive toxicity, irritation, allergic response,
or other problem or complication, commensurate with a
15 reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts"
refer to derivatives of the disclosed compounds wherein the
parent compound is modified by making acid or base salts
thereof. Examples of pharmaceutically acceptable salts
20 include, but are not limited to, mineral or organic acid
salts of basic groups such as amines; and alkali or organic
salts of acidic groups such as carboxylic acids. The
pharmaceutically acceptable salts include the conventional
non-toxic salts or the quaternary ammonium salts of the
25 parent compound formed, for example, from non-toxic
inorganic or organic acids. For example, such conventional
non-toxic salts include those derived from inorganic acids
such as hydrochloric, hydrobromic, sulfuric, sulfamic,
phosphoric, and nitric; and the salts prepared from organic
30 acids such as acetic, propionic, succinic, glycolic,
stearic, lactic, malic, tartaric, citric, ascorbic, pamoic,
maleic, hydroxymaleic, phenylacetic, glutamic, benzoic,
salicylic, sulfanilic, 2-acetoxybenzoic, fumaric,
toluenesulfonic, methanesulfonic, ethane disulfonic,
35 oxalic, and isethionic.

The pharmaceutically acceptable salts of the present
invention can be synthesized from the parent compound which
contains a basic or acidic moiety by conventional chemical
methods. Generally, such salts can be prepared by reacting
40 the free acid or base forms of these compounds with a
stoichiometric amount of the appropriate base or acid in
water or in an organic solvent, or in a mixture of the two;

5 generally, nonaqueous media like ether, ethyl acetate,
ethanol, isopropanol, or acetonitrile are preferred. Lists
of suitable salts are found in *Remington's Pharmaceutical*
Sciences, 17th ed., Mack Publishing Company, Easton, PA,
1985, p. 1418, the disclosure of which is hereby
10 incorporated by reference.

Since prodrugs are known to enhance numerous desirable
qualities of pharmaceuticals (e.g., solubility,
bioavailability, manufacturing, etc.) the compounds of the
present invention may be delivered in prodrug form. Thus,
15 the present invention is intended to cover prodrugs of the
presently claimed compounds, methods of delivering the same
and compositions containing the same. "Prodrugs" are
intended to include any covalently bonded carriers which
release an active parent drug of the present invention *in*
20 *vivo* when such prodrug is administered to a mammalian
subject. Prodrugs of the present invention are prepared by
modifying functional groups present in the compound in such
a way that the modifications are cleaved, either in routine
manipulation or *in vivo*, to the parent compound. Prodrugs
25 include compounds of the present invention wherein a
hydroxy, amino, or sulfhydryl group is bonded to any group
that, when the prodrug of the present invention is
administered to a mammalian subject, it cleaves to form a
free hydroxyl, free amino, or free sulfhydryl group,
30 respectively. Examples of prodrugs include, but are not
limited to, acetate, formate and benzoate derivatives of
alcohol and amine functional groups in the compounds of the
present invention.

"Stable compound" and "stable structure" are meant to
35 indicate a compound that is sufficiently robust to survive
isolation to a useful degree of purity from a reaction
mixture, and formulation into an efficacious therapeutic
agent.

"Therapeutically effective amount" is intended to
40 include an amount of a compound of the present invention or
an amount of the combination of compounds claimed effective
to inhibit HCV infection or treat the symptoms of HCV

5 infection in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, 22, 27-55, occurs when the effect (in this case, inhibition of the desired target) of the compounds
10 when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity,
15 increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

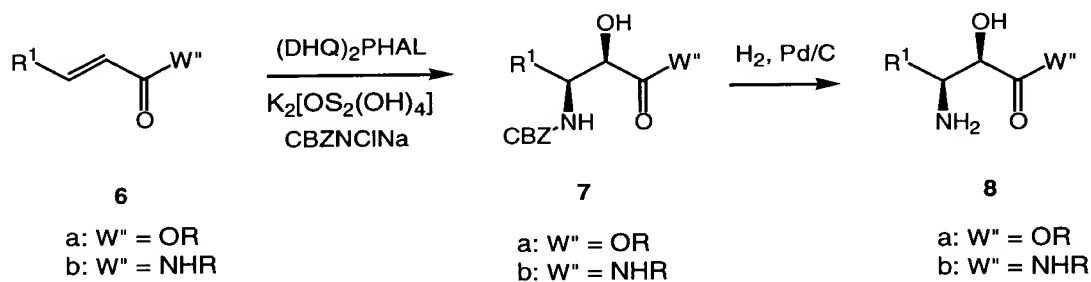
SYNTHESIS

20 The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as
25 appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

30 The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in
35 the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the
40 conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is

5 prepared from commercially available materials. Sharpless
 asymmetric aminohydroxylation of α,β -unsaturated ester or
 amide **6** gives α -hydroxyl β -amino ester or α -hydroxyl β -
 amino amide **7**. Reductive removal of the carbobenzyloxy
 (CBZ) group provides **8**. (Sharpless, K. B.; et al, *Angew.*
 10 *Chem. Int. Ed. Engl.* **1996**, 35, 451. Sharpless, K. B. et
 al, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2813.)

Scheme 2

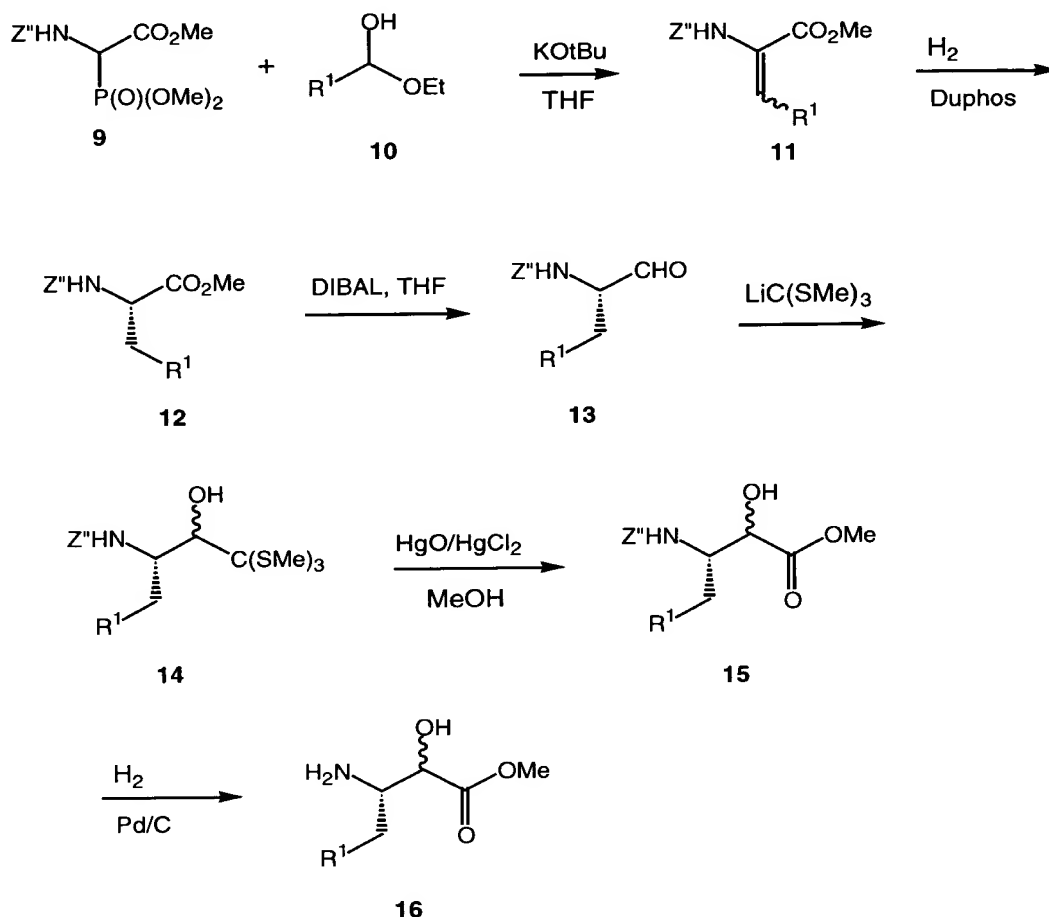


15

A series of α -hydroxyl β -amino esters of formula **15**
 are prepared by the method outlined in Scheme 3. Treatment
 of phosphonoglycine trimethyl ester **9**, wherein Z'' is an
 amino protecting group such as CBZ, with
 20 difluoroacetaldehyde hemiacetal **10** in the presence of KOTBu
 yields α,β -unsaturated ester **11**. Hydrogenation of **11** in
 the presence of a chiral Rh catalyst, such as Duphos,
 selectively reduces the double bond and affords **12** in high
 enantiomeric excess. DIBAL reduction of methyl ester **12**
 25 gives corresponding aldehyde **13**, which under the treatment
 of lithium tris(methylthio)methane to provide α -hydroxyl
 compound **14**. Finally, α -hydroxyl β -amino ester of formula
15 is obtained when **14** is treated with Hg^{2+} . (Kaneko, S.
 K.; et al, *J. Org. Chem.* **1993**, 58, 2302.)

30

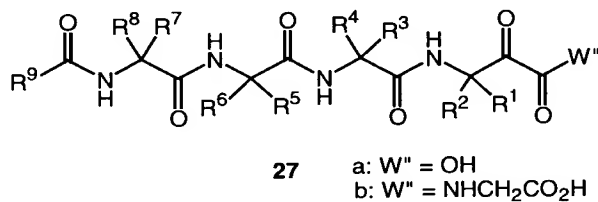
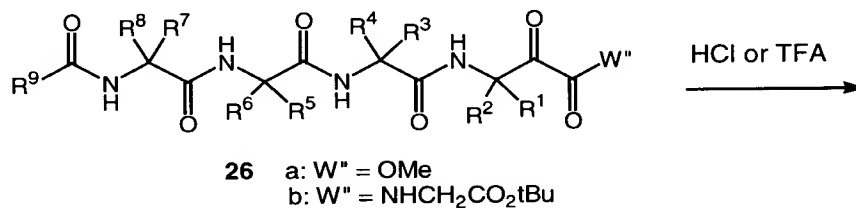
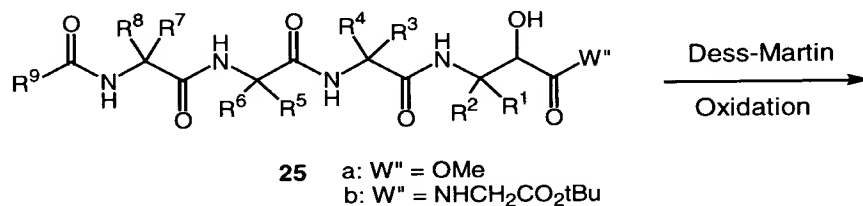
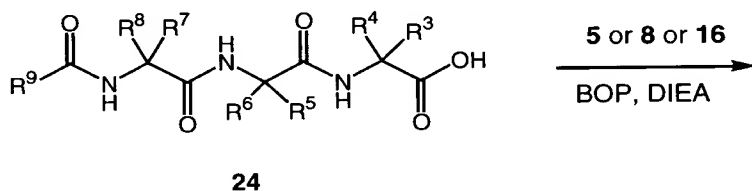
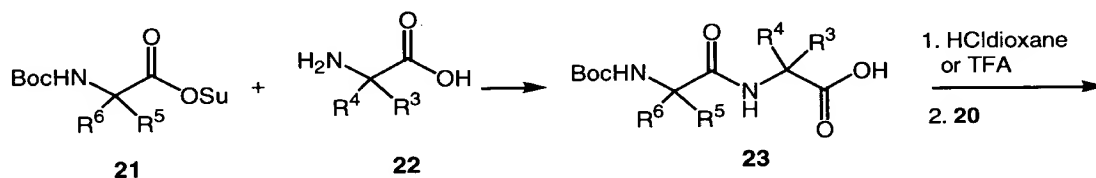
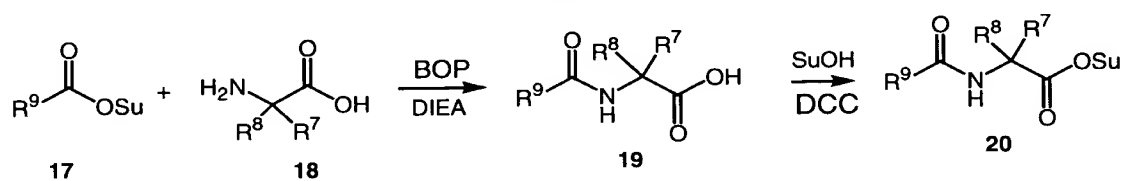
Scheme 3



A series of α -ketoamides or acids of formula **27** are prepared by the method outlined in Scheme 4. Amino acid **18** is coupled with **17** under regular coupling conditions to afford **19**, which is then converted to its succinimide **20**. Compound **20** is coupled with dipeptide **23**, which is prepared by the same method, to yield tripeptide **24**. Compound **24** is reacted with the α -hydroxyl β -amino ester or amide under standard coupling conditions to give α -hydroxyl ester or amide **25**. Dess-Martin oxidation converts **25** to α -keto ester or amide **26**. The methyl ester **26** is either saponified to provide α -keto acid **27a**, or deprotected in

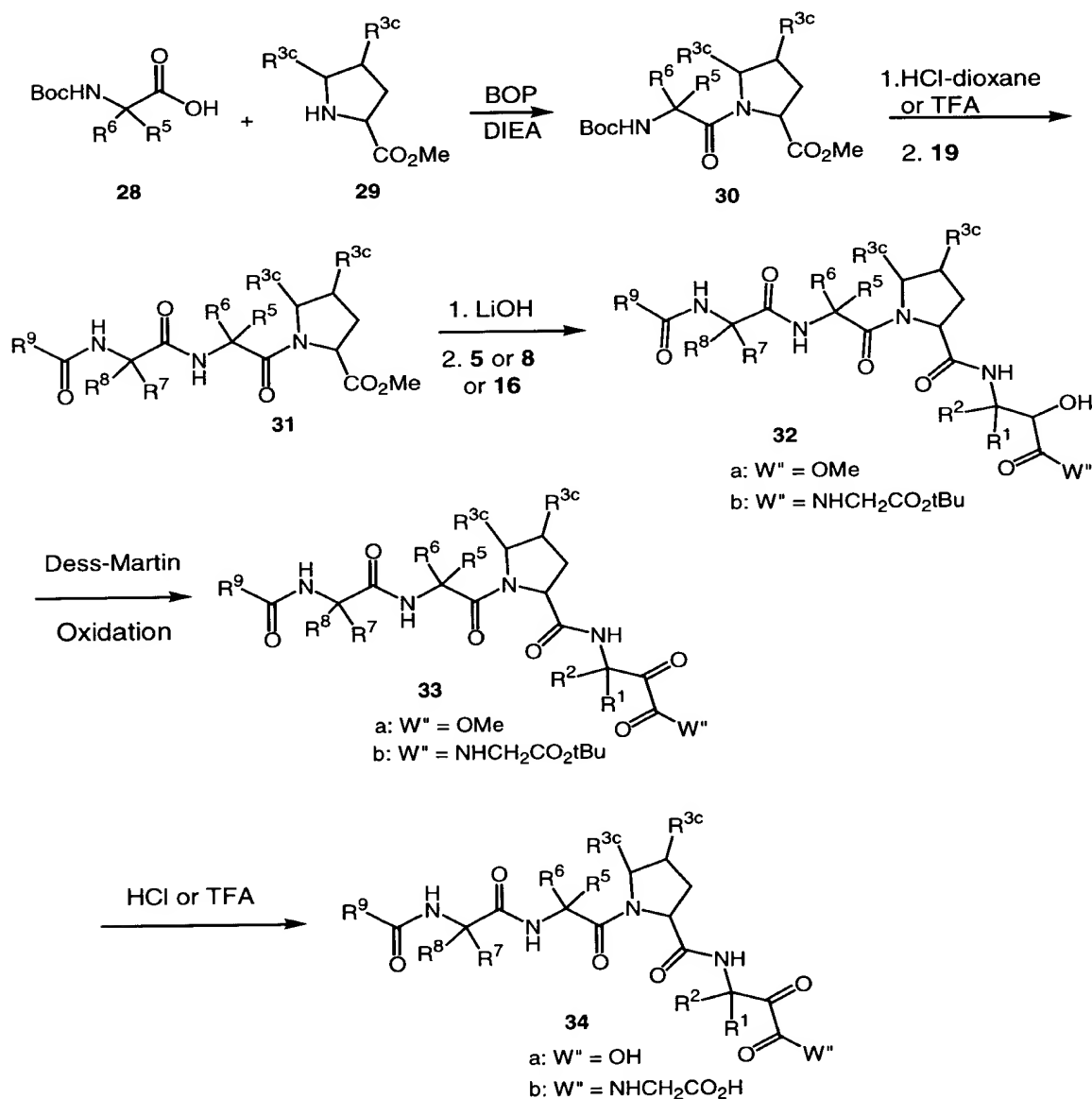
- 5 TFA to afford α -keto amide **27b**. (Angelastro,, M. R. *J. Med. Chem.* **1990**, 33, 13.)

Scheme 4



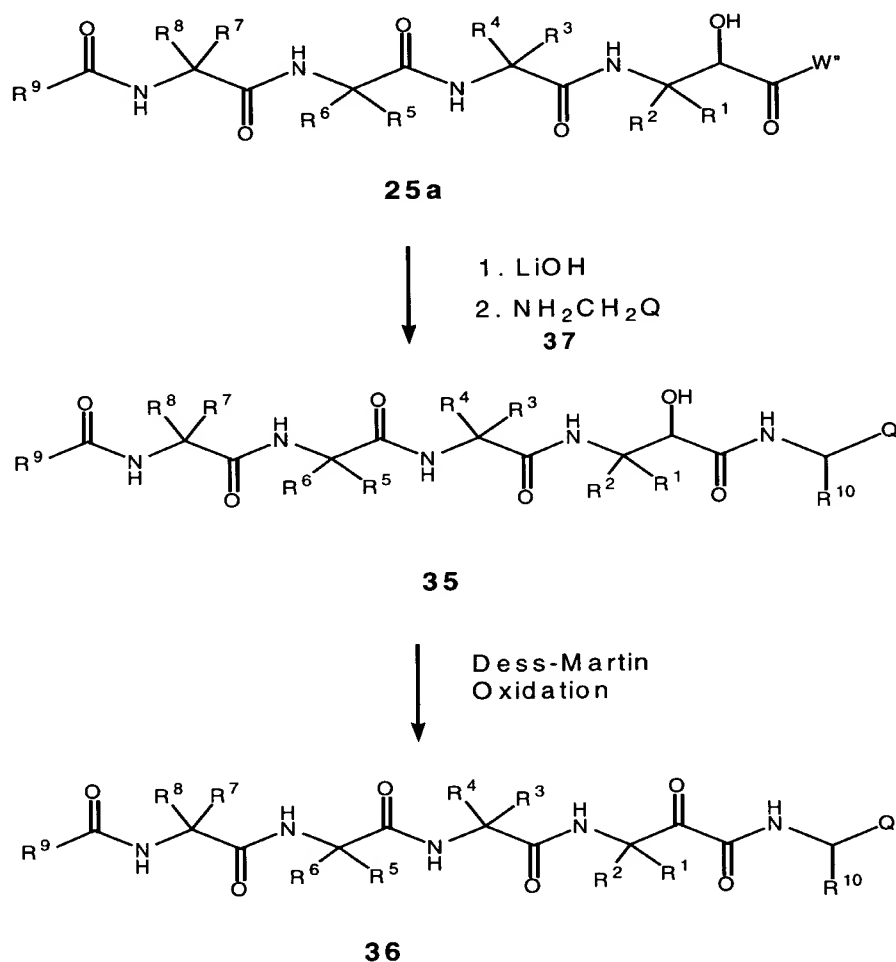
5 A series of α -keto amides or acids of formula **34** are prepared by the method outlined in Scheme 5. Coupling of acid **28** with proline derivative **29** in the presence of BOP and DIEA yields compound **30**. Deprotection of BOC group in **30** followed by the coupling with the same intermediate **19** provides compound **31**. Application of similar chemistry to that described in Scheme 4 leads to the synthesis of α -keto amides or acids of formula **34**.

Scheme 5



5 A series of α -ketoamides of formula **36** are prepared by
the method outlined in Scheme 6. From the same
intermediate **25a**, saponification affords the corresponding
acid, which reacts with amines of formula **37** to give α -
hydroxyamide **35**. Dess-Martin oxidation of **35** provides α -
10 ketoamide **36**.

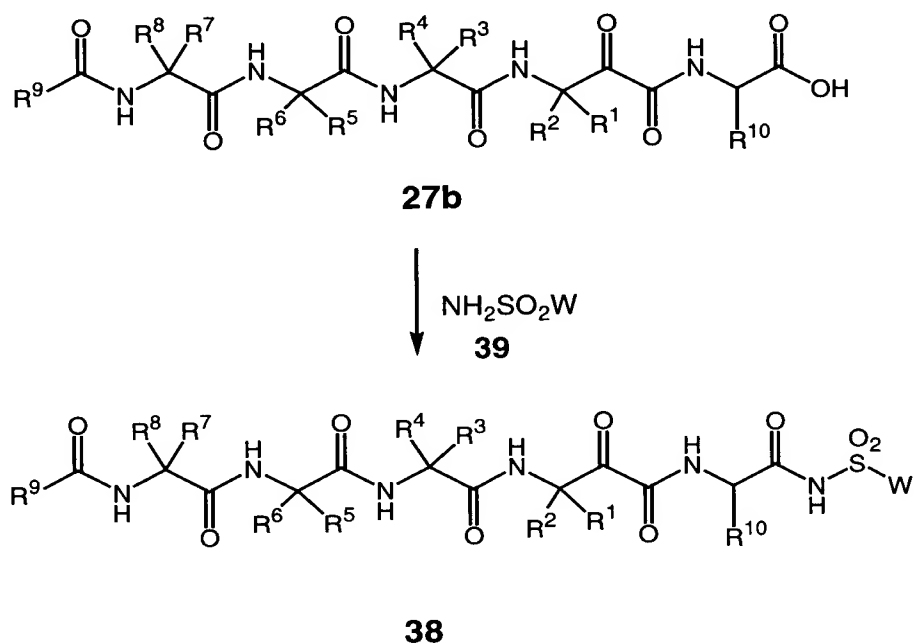
Scheme 6



15

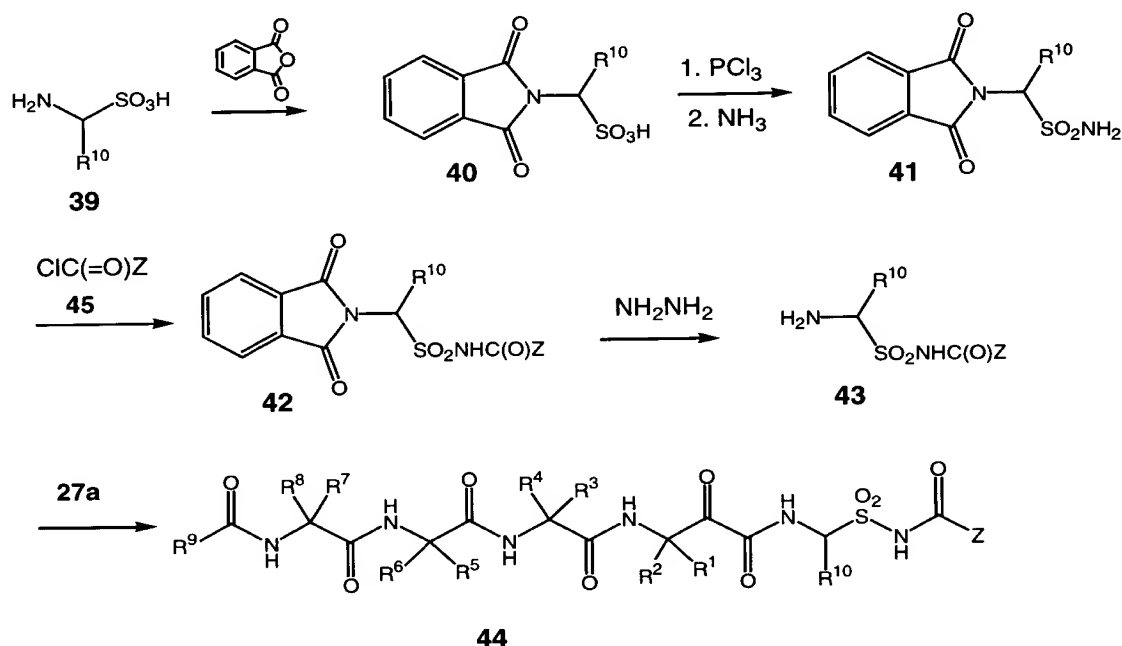
A series of α -ketoamides of formula **38** are prepared by
the method outlined in Scheme 7. Treatment of intermediate
27b with sulfonamide of type **39** in the presence of a
coupling agent such as EDCI and DMAP provides α -ketoamide
20 **38**. (Andery, R. H.; J. Org. Chem. 1986, 987).

Scheme 7



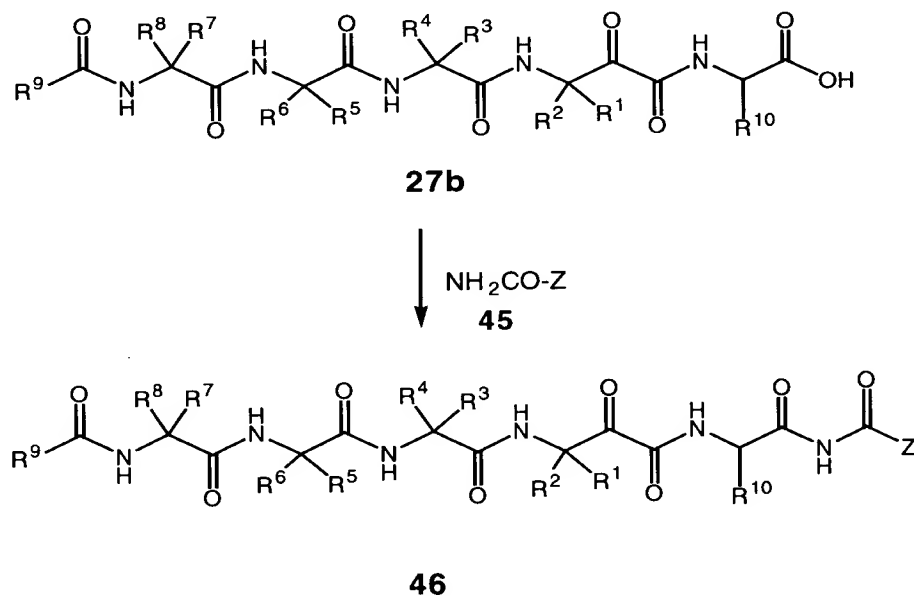
- 10 A series of α -ketoamides of formula **44** are prepared by the method outlined in Scheme 8. Protection of the amino group in **39** gives sulfonic acid **40**. Treatment of compound **40** with PCl_3 followed by ammonia yields sulfonamide **41**. Acylation of **41** with an acid chloride of type **45** affords
- 15 acyl sulfonamide **42**. Deprotection of the N terminal **42** with hydrazine gives amine **43**. Coupling of amine **43** with α -ketoacid **27a** provides α -ketoamide **44**.

Scheme 8



A series of α -ketoamides of formula **46** are prepared by the method outlined in Scheme 9. Treatment of intermediate **27b** with amide of type **45** in the presence of DCC and DMAP provides α -ketoamide **46**. (Almeida, P. S. et al. *Tetrahedron Lett.* **1991**, 23, 2671).

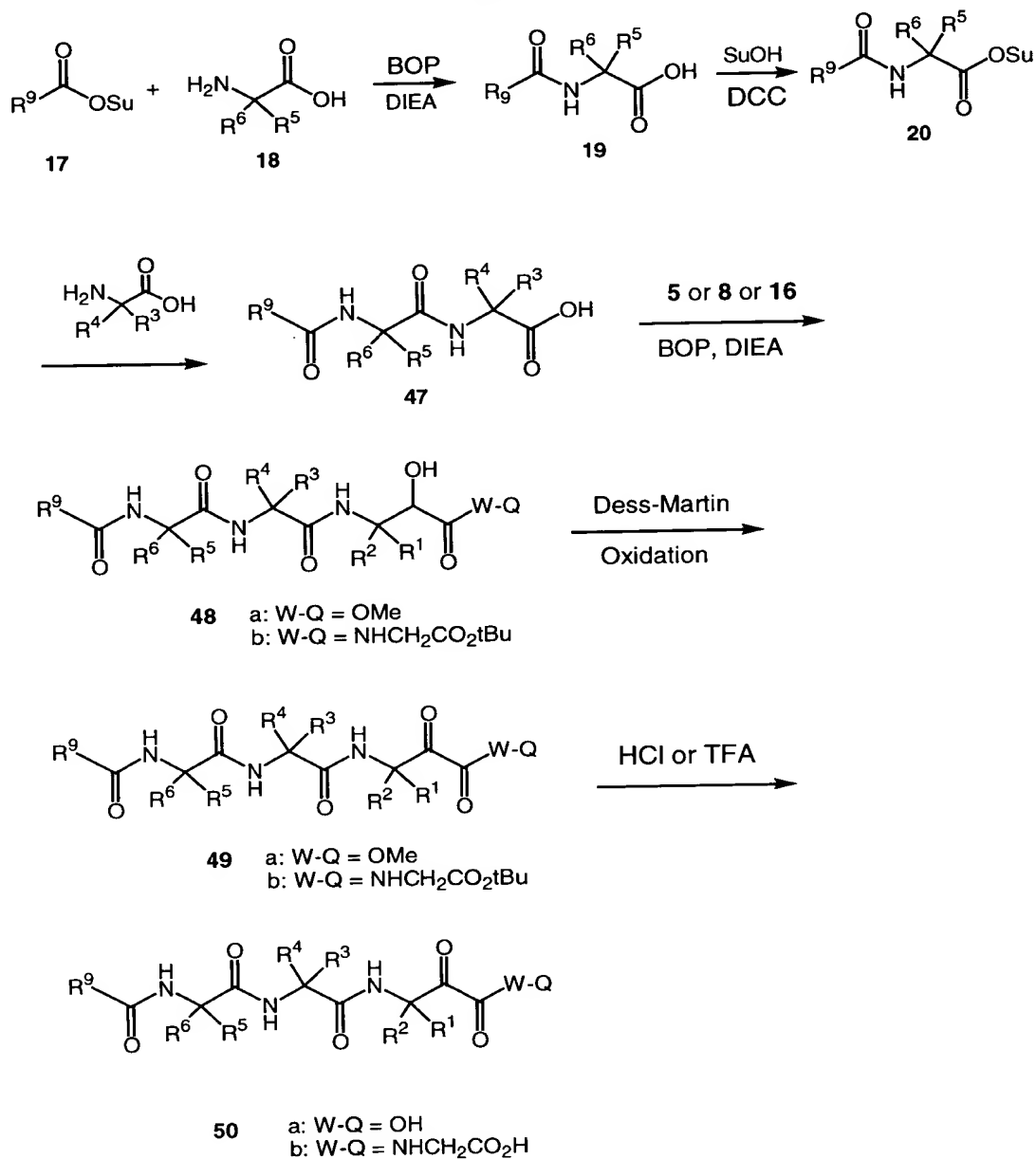
Scheme 9



A series of α -ketoamides of formula **50** are prepared by a similar method to the preparation of compound **27** as outlined in Scheme 10.

Many of the CBZ protected amino acids and amino acid methyl esters are commercially available or may be prepared from commercial amino acid derivatives by simple protecting group manipulations. Others may be synthesized in racemic form using the Strecker synthesis or amidomalonate synthesis. In addition, the Myers pseudoephedrine glycinamide alkylation method (Myers, A. G.; Gleason, J. L.; Yoon, T; Kung, D. W.. *J. Am. Chem. Soc.* **1997**, *119*, 656-673) and the Evans electrophilic azidation (Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011) may be used to prepare unnatural amino acids in enantiomerically pure form.

Scheme 10



When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotherapy* **1995**, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet. lett.* **1995**, 36, 8937-8940).

5 Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Examples

10 Abbreviations used in the examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "rt" for room temperature, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or
15 milliliters, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "MS" for mass spectrometry, "NMR" for nuclear magnetic resonance spectroscopy, "¹H" for proton, "HPLC" for high pressure liquid chromatography, "tlc" for thin
20 layer chromatography, "v/v" for volume to volume ratio, "atm" for atmosphere, "α", "β", "R", and "S" are stereochemical designations familiar to one skilled in the art.

Abbreviations used in the specification are defined as
25 follows:

"BOP" is benzotriazol-1-yloxy-tris(dimethylamino)-
phosphonium hexafluorophosphate;
"Bzl" or "Bn" is benzyl;
"CBZ" is carbobenzyloxy;
30 "COD" is cyclooctadiene;
"DCC" is 1,3-dicyclohexylcarbodiimide;
"(DHQ)₂PHAL" is hydroquinine 1,4-phthalazinediyl
diether;
"DIBAL" is diisobutylaluminum hydride;
35 "DIEA" is Diisopropylethylamine;
"DMAP" is 4-dimethylamino pyridine;
"DMF" is dimethylformamide ;
"DMSO" is dimethylsulfoxide;
"Duphos" is (+)-1,2-bis(2S,5S)-2,5-
40 diethylphospholano)-

5 benzene(cyclooctadiene)rhodium(I)
trifluoromethanesulfonate
"EtOAc" is ethylacetate;
"EDCI" is 1-(3-dimethylaminopropyl)-3-
ethylcarbodiimide hydrochloride;
10 "Pz" is pyrazinyl;
"SuOH" is N-hydroxysuccinimide; and
"TFA" is trifluoroacetic acid.

Example A1

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3 S)-3-amino pentanoylglycine

Step (A1a): At 0°C, DIEA (12.1mL, 69.5 mmol) was added to
the suspension of Ph₃PCH₂CNCl in CH₂Cl₂. The suspension
20 turned to clear. The aminobutyric acid (15.0g, 63.2 mmol)
was added followed by addition of EDCI (12.7g, 66.4 mmol)
and DMAP (0.77g, 6.32 mmol). The resulted mixture was
stirred at 0°C for 2h and at rt over night. Most of the
solvent was evaporated and the residue was chromatographed
25 on silica gel (50-60% EtOAc:Hexane). The product (Scheme
1, 2) was obtained as a white solid 22.7g in 69% yield. MS
found (M+1)⁺ 521.3

Step (A1b): The ylide obtained from Step(A1a) (10g, 19.2
30 mmol) was dissolved in CH₂Cl₂ (200 mL) and the mixture was
cooled to -78°C. To this mixture at -78°C was purged O₃
until the color changed to blue. Excess O₃ was removed by
purging N₂ into the mixture. The solution of Gly-OtBu
hydrochloride (3.54g, 21.1 mmol), pretreated with DIEA and
35 precooled) in CH₂Cl₂ was added at -78°C to the above
reaction mixture and stirred at -78°C for 30 min, then
warmed to rt. Solvent was evaporated and the residue was
chromatographed on silica gel (20-50% EtOAc:hexane). The
α-ketoamide (Scheme 1, 3) was obtained in 58% yield as an
40 oil (4.25g). MS found (M+Na)⁺ 401.1. Similarly, the

5 reaction mixture can be quenched with methanol instead of Gly-OtBu to provide the corresponding α -ketoester (Scheme 1, **3a**).

Step (A1c): To a solution of ketoamide obtained from Step
10 (A1b) (0.23g, 0.61 mmol) in THF (10 mL) at 0°C was added sodium borohydride (42mg, 1.22mmol) in portions. After stirring at 0°C for 30 min, the reaction mixture was quenched with acetone. Most of the solvent was evaporated and the residue was dissolved in EtOAc, washed with H₂O and
15 brine. Chromatography on silica gel (40% EtOAc in hexane) yielded 124 mg α -hydroxyamide (Scheme 1, **4**) as a colorless oil (53%). MS found (M+1)⁺ 381.2.

Step (A1d): The α -hydroxyamide obtained from Step (A1c)
20 (124 mg, 0.326 mmol) was dissolved in MeOH (50 mL) and Pd/C (10mg) was added. The mixture was hydrogenated under 1 atm. for 40 min. The reaction mixture was filtered and concentrated. The amine (Scheme 1, **5**) was obtained in 99% yield as a white solid 82 mg. MS found (M+1)⁺ 247.3.
25 Similarly, the α -ketoester from (A1b) was converted to α -hydroxyester (Scheme 1, **5a**) via step (A1c).

Step (A1e): DCC (3.99g, 19.3 mmol, 1.2 eq) was added to a solution of 2-pyrazine carboxylic acid (2.0g, 16.1 mmol)
30 and N-hydroxysuccinimide (1.95g, 16.9 mmol, 1.05eq) in 100mL THF at 0°C. The mixture was stirred at rt over night. The reaction mixture was filtered, concentrated and dried. The product was obtained in 91% yield as a solid (Scheme 4, **17**).

35 Step (A1f): At 0°C under N₂, DIEA (13.3mL, 76.13 mmol) was added to a solution of material from Step (A1e) (10g, 45.2 mmol) and leucine (5.93g, 45.3 mmol) in 120 mL DMF. After addition, the resulted mixture was stirred at rt over
40 night. The mixture was diluted with 200 mL of EtOAc,

5 washed with 1N HCl (2x30 mL), H₂O (2x50 mL) and brine, and dried over MgSO₄. The solvent was removed and dried on vacuum to provide a white solid as pure product (95%) (Scheme 4, **19**). MS found (M-1)⁻ 219.

10 Step (A1g): Following a procedure analogous to Step (A1e), the material from Step (A1f) (1.0g, 4.5 mmol) was treated with N-hydroxysuccinimide (530 mg, 4.5 mmol), providing the desired product as a white solid (1.28g, 90%) (Scheme 4, **20**).

15 Step (A1h): Following a procedure analogous to Step (A1f), the succinimide ester of N-Boc isoleucine (10g, 30.45 mmol) was treated with cyclohexylalanine (6.32g, 30.45 mmol) in the presence of DIEA in DMF, providing the desired product
20 (Scheme 4, **23**) as a white solid (95%). MS found (M+1)⁺ 385.3.

Step (A1i): The material from Step (A1h) (1.0g, 2.6 mmol) was treated with 4M HCl in dioxane for 2h at rt. Solvent
25 was evaporated and the residue was dried. Following a procedure analogous to Step (A1f), the material from above was treated with the material from Step (A1g) (0.83g, 2.6 mmol) in the presence of DIEA in DMF, providing the desired product (Scheme 4, **24**) as a white solid (1.16g, 89%). MS
30 found (M+1)⁺ 504.3.

Step (A1j): To a solution of the above material from Step (A1i) (1g, 1.99 mmol) in 100mL of DMF at 0°C was added BOP (1.3g, 2.98 mmol) and DIEA (0.52 mL, 2.98 mmol). The
35 mixture was stirred at this temp. for 20 min. Then a solution of the material from Step (A1d) (490 mg, 1.99 mmol) in 10 mL of DMF was added to the above mixture followed by addition of another portion of DIEA (0.52 mL, 1.99 mmol). The resulting mixture was stirred at 0°C for
40 1h and rt overnight. The reaction mixture was diluted with EtOAc (400 mL), washed with 1N HCl, saturated NaHCO₃, H₂O,

5 brine, dried and concentrated. Chromatography on silica gel (70% EtOAc in hexane) provided desired product (1.22g, 84%) as a white solid (Scheme 4, **25b**). MS found (M+1)⁺ 732.4.

10 Step (A1k): To a mixture of the above material from Step (A1j) (200 mg, 0.27 mmol) and molecular sieves in 6 mL of CH₂Cl₂ was added Dess-Martin reagent (172 mg, 0.41 mmol). The resulting mixture was stirred at rt for 2h. Then the mixture was filtered and the residue was chromatographed on
15 silica gel (5% MeOH in CHCl₃) to provide the desired ketoamide (Scheme 4, **26b**) as a white solid (169mg, 86%). MS found (M+1)⁺ 730.3.

Step (A1l): A solution of the above material from Step
20 (A1k) (300 mg, 0.41 mmol) in CH₂Cl₂ was treated with TFA (20 mL, 1:1) and the mixture was stirred at rt for 2h. After evaporation of the solvent, the residue was dried in vacuum and the title ketoamide (Scheme 4, **27b**), Example 1A, was obtained (273 mg, 99%) as a light yellow solid. MS
25 found (M+1)⁺ 674.4.

Example A2

(3S)-2-oxo-3-{[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino}-N-(2H-tetrazol-5-ylmethyl) pentanamide
30

Step (A2a): The ylide obtained from Step (A1a) (10g, 19.2 mmol) was dissolved in CH₂Cl₂ (200 mL) and the mixture was cooled to -78°C. To this mixture was purged O₃ at this
35 temp. until the color of the mixture changed to blue. Excess O₃ was removed by purging N₂ into the mixture. Methanol was added at -78°C to the above reaction mixture. The resulting mixture was stirred at -78°C for 30 min and warmed to rt. Solvent was evaporated and the residue was
40 chromatographed on silica gel (20-50% EtOAc:hexane). The

5 α -ketoester (Scheme 1, **3a**) was obtained in 87% yield as a white solid. MS found (M+Na)⁺ 280.4.

Step (A2b): Following a procedure analogous to Step (A1c), the ketoester from Step (A2a) (1g, 3.6 mmol) was reduced
10 with NaBH₄ to the desired α -hydroxyester (Scheme 1, **4a**) as a white solid (0.86g, 86%). MS found (M+1)⁺ 282.3.

Step (A2c): Following a procedure analogous to Step (A1d), the α -hydroxyester (0.7g, 2.5 mmol) from Step (A2b) above
15 was hydrogenated in the present of 10% Pd/C to give the desired amine (Scheme 1, **5a**) as a white solid (3.6g, >95%). MS found (M+1)⁺ 148.3.

Step (A2d): Following a procedure analogous to Step (A1j),
20 the material from Step (A2c) above (0.5g, 3.4 mmol) was coupled with the material from Step (A1i) (1.7g, 3.4 mmol) to provide the desired the α -hydroxyester (Scheme 4, **25a**) as a white solid (1.4g, 67%). MS found (M+1)⁺ 633.3.

25 Step (A2e): To a solution of the above material from Step (A2d) (500 mg, 0.79 mmol) in 8 mL THF at 0°C was added 8mL of 1N LiOH solution. After stirring at this temp for 3h, the mixture was acidified with 1N HCl to pH 5. Solvent was evaporated and the residue was extrated with EtOAc (3x50
30 mL). The combined organic portion was washed with water, brine and dried. Removal of solvent yielded the acid product (463mg, 95%) as white solid. MS found (M+1)⁺ 619.2, (M-1)⁻ 617.1.

35 Step (A2f): Aminomethyltetrazole (75 mg, 0.76 mmol) was suspended in 6 mL mixed solvent of DMF/DMSO (1:1). To this mixture was added DIEA (0.3 mL), material from Step (A2e) above (50 mg, 0.081 mmol) and BOP reagent (200 mg). The resulting mixture was stirred at rt for 3h. Then the
40 mixture was HPLC purified (grandient starting from 30%

5 water in acetonitrile) to give the desired product as a white solid (46mg, 82%). MS found (M+1)⁺ 701.4.

Step (A2g): The material from Step (A2f) above (46 mg, 0.066 mmol) was dissolved in 5.0 mL methylenechloride. 10 Dess-Martin reagent (100 mg) was added. The mixture was stirred at rt for 1.5h. Then the reaction mixture was filtered and solvent was removed. HPLC purification (gradient starting from 30% water in acetonitrile) gave Example A2, a white solid, as pure product (40mg, 89%). MS 15 found (M+1)⁺ 698.4.

Example A3

2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl]amino]-N-(sulfomethyl)pentanamide

20 Step (A3a): Following a procedure analogous to Step (A2f), the material from Step (A2e) (50 mg, 0.081 mmol) was coupled with aminomethanesulfonic acid (18 mg, 0.16 mmol), providing the title product as a light-yellow solid (44mg, 25 76%). MS found (M+1)⁺ 712.3.

Step (A3b): Following a procedure analogous to Step (A2g), the above material from Step (3a) (44mg, 0.062 mmol) was oxidized with Dess-Martin reagent to give the title α- 30 ketoamide (30mg, 68%). MS found (M+1)⁺ 710.3.

Example A4

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(2-nitrophenyl) 35 sulfonyl]glycinamide

Step (A4a): To the mixture of the material from Step (A11) (Scheme 4, **27b**) (34 mg, 0.05 mmol) in CH₂Cl₂ (5mL) at 0°C were added a solution of (2-nitrophenyl)sulfonamide (15 mg, 40 0.075 mmol) and DMAP (6mg, 0.05mmol) in CH₂Cl₂, followed by addition of EDCI (14.3 mg, 0.075 mmol). The resulting

5 mixture was stirred at rt for 40 min. The reaction mixture was diluted with EtOAc, washed with H₂O, brine, dried and concentrated. HPLC purification gave the title product as a white solid. MS found (M+1)⁺ 858.3.

10

Example A5

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(methylsulfonyl)glycinamide

15 Step (A5a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with methylsulfonamide to provide the title compound. MS found (M+1)⁺ 751.4.

Example A6

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(phenylmethyl)sulfonyl]glycinamide

25 Step (A6a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with phenylmethylsulfonamide to provide the title compound. MS found (M+1)⁺ 825.4.

Example A7

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(phenylsulfonyl)glycinamide

35 Step (A7a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with phenylsulfonamide to provide the title compound. MS found (M+1)⁺ 813.4.

Example A8

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(trifluoromethyl)sulfonyl]glycinamide

5

Step (A8a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with trifluoromethylsulfonamide to provide the title compound. MS found (M+1)⁺ 805.4.

10

Example A9

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-nitrophenyl)sulfonyl]glycinamide

15

Step (A9a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (2-nitrophenyl)sulfonamide to provide the title compound. MS found (M+1)⁺ 858.1.

20

Example A10

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-nitrophenyl)sulfonyl]glycinamide

25

Step (A10a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-nitrophenyl)sulfonamide to provide the title compound. MS found (M+1)⁺ 858.3.

30

Example A11

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-fluorophenyl)sulfonyl]glycinamide

35

Step (A11a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-fluorophenyl)sulfonamide to provide the title compound. MS found (M+1)⁺ 831.4.

40

5

Example A12

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-fluorophenyl)sulfonyl]glycinamide

10 Step (A12a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (3-fluorophenyl)sulfonamide to provide the title compound. MS found (M+1)⁺ 831.4.

15

Example A13

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2-fluorophenyl) sulfonyl]glycinamide

20 Step (A13a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (2-fluorophenyl)sulfonamide to provide the title compound. MS found (M+1)⁺ 831.5.

25

Example A14

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chlorophenyl) sulfonyl]glycinamide

30 Step (A14a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (4-chlorophenyl)sulfonamide to provide the title compound. MS found (M+1)⁺ 848.3.

35

Example A15

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentano yl-N-[(3-chlorophenyl) sulfonyl]glycinamide

40 Step (A15a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (3-

5 chlorophenyl)sulfonamide to provide the title compound. MS
found (M+1)⁺ 848.4.

Example A16

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-
(thionitroso) phenyl]sulfonyl]glycinamide

Step (A16a) Following a procedure analogous to Step (A4a),
compound **27b** (Scheme 4) was coupled with 4-
15 (thionitroso)phenylsulfonamide to provide the title
compound. MS found (M+1)⁺ 870.6.

Example A17

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-
[(trifluoromethyl)sulfonyl]phenyl]sulfonyl]glycinamide

Step (A17a) Following a procedure analogous to Step (A4a),
compound **27b** (Scheme 4) was coupled with 4-
25 [(trifluoromethyl)sulfonyl]phenyl-sulfonamide to provide
the title compound. MS found (M+1)⁺ 946.1.

Example A18

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[4-
(trifluoromethyl)phenyl]sulfonyl]glycinamide

Step (A18a) Following a procedure analogous to (4a),
compound **27b** (Scheme 4) was coupled with 4-
35 (trifluoromethyl)-phenylsulfonamide to provide the title
compound. MS found (M+1)⁺ 881.8.

Example A19

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-
cyanophenyl)sulfonyl]glycinamide

5

Step (A19a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-cyanophenylsulfonamide to provide the title compound. MS found (M+1)⁺ 839.0.

10

Example A20

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3-chloro-4-methylphenyl)sulfonyl]glycinamide

15

Step (A20a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-chloro-4-methylphenylsulfonamide to provide the title compound. MS found (M+1)⁺ 862.3.

20

Example A21

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-chloro-3-nitrophenyl)sulfonyl]glycinamide

25

Step (A21a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-chloro-3-nitrophenylsulfonamide to provide the title compound. MS found (M+1)⁺ 893.4.

30

Example A22

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichlorophenyl)sulfonyl]glycinamide

35

Step (A22a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3,5-dichlorophenylsulfonamide to provide the title compound. MS found (M+1)⁺ 882.9.

40

5

Example A23

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(4-methyl-3-nitrophenyl)sulfonyl]glycinamide

- 10 Step (A23a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-methyl-3-nitrophenylsulfonamide to provide the title compound. MS found (M+1)⁺ 873.1.

15

Example A24

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-(trifluoromethyl)phenyl]sulfonyl]glycinamide

- 20 Step (A24a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-(trifluoromethyl)phenyl-sulfonamide to provide the title compound. MS found (M+1)⁺ 916.5.

25

Example A25

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide

- 30 Step (A25a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-carboxy-2-chlorophenylsulfonamide to provide the title compound. MS found (M+1)⁺ 892.3.

35

Example A26

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(2,5-dichlorophenyl)sulfonyl]glycinamide

- 40 Step (A26a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2,5-

5 dichlorophenylsulfonamide to provide the title compound. MS
found (M+1)⁺ 879.5.

Example A27

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,4-
difluorophenyl)sulfonyl]glycinamide

Step (A27a) Following a procedure analogous to Step (A4a),
compound **27b** (Scheme 4) was coupled with 3,4-
15 difluorophenylsulfonamide to provide the title compound. MS
found (M+1)⁺ 849.6.

Example A28

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(3,5-dichloro-
2-hydroxyphenyl)sulfonyl]glycinamide

Step (A28a) Following a procedure analogous to Step (A4a),
compound 27b (Scheme 4) was coupled with 3,5-dichloro-2-
25 hydroxyphenylsulfonamide to provide the title compound. MS
found (M-1)⁻ 895.5.

Example A29

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[(2,4,5-
trichlorophenyl)-sulfonyl]glycinamide

Step (A29a) Following a procedure analogous to Step (A4a),
compound **27b** (Scheme 4) was coupled with 2,4,5-
35 trichlorophenylsulfonamide to provide the title compound.
MS found (M-1)⁻ 913.3.

Example A30

40 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(5-carboxy-4-
chloro-2-fluorophenyl)sulfonyl]glycinamide

5

Step (A30a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-carboxy-4-chloro-2-fluorophenyl sulfonamide to provide the title compound. MS found (M+1)⁺ 910.6.

10

Example A31

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]glycinamide

15

Step (A31a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-(dimethylamino)-1-naphthalenylsulfonamide to provide the title compound. MS found (M+1)⁺ 907.3.

20

Example A32

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-(2-naphthalenylsulfonyl)glycinamide

25

Step (A32a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-naphthalenylsulfonamide to provide the title compound. MS found (M+1)⁺ 864.2.

30

Example A33

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L- alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[(4-(phenyl)phenyl)-sulfonyl]glycinamide

35

Step (A33a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 4-biphenylsulfonamide to provide the title compound. MS found (M+1)⁺ 889.5.

40

5

Example A34

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[(6-ethoxy-2-benzothiazolyl)sulfonyl]glycinamide

- 10 Step (A34a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with (6-ethoxy-2-benzothiazolyl)sulfonamide to provide the title compound. MS found (M+1)⁺ 915.2.

15

Example A35

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl- N-[[2-chloro-5-[(phenylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

- 20 Step (A35a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-[[[(phenylmethyl)amino]carbonyl]-phenyl sulfonamide to provide the title compound. MS found (M+1)⁺ 980.6.

25

Example A36

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[(2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

- 30 Step (A36a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with [(2-trifluoroethyl)amino]carbonyl]phenyl sulfonamide to provide the title compound. MS found (M-1)⁻ 970.5.

35

Example A37

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-5-[(cyclopropylmethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

40

5 Step (A37a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-5-[[[(cyclopropylmethyl)amino]-carbonyl]phenyl] sulfonamide to provide the title compound. MS found (M+1)⁺ 944.4.

10

Example A38

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-nitro-4-(2-pyrimidinylthio)phenyl]sulfonyl]glycinamide

15

Step (A38a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-nitro-4-(2-pyrimidinylthio)phenyl sulfonamide to provide the title compound. MS found (M+1)⁺ 968.4.

20

Example A39

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[2-chloro-4-(acetylamino)phenyl]sulfonyl]glycinamide

25

Step (A39a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 2-chloro-4-(acetylamino)phenyl sulfonamide to provide the title compound. MS found (M-1)⁻ 902.5.

30

Example A40

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-chloro-4-(2-benzoxazolylthio)phenyl]sulfonyl]glycinamide

35

Step (A40a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-chloro-4-(2-benzoxazolylthio)phenyl sulfonamide to provide the title compound. MS found (M-1)⁻ 1005.5.

5

Example A41

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3,5-dichloro-4-(4-nitrophenoxy)phenyl]sulfonyl]glycinamide

- 10 Step (A41a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3,5-dichloro-4-(4-nitrophenoxy)phenyl sulfonamide to provide the title compound. MS found (M+1)⁺ 1018.5.

15

Example A42

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]glycinamide

- 20 Step (A42a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 5-(acetylamino)-1,3,4-thiadiazol-2-yl sulfonamide to provide the title compound. MS found (M+1)⁺ 878.5.

25

Example A43

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[(3-cyanophenyl)sulfonyl]glycinamide

- 30 Step (A43a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-cyanophenylsulfonamide to provide the title compound. MS found (M+1)⁺ 838.4.

35

Example A44

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3 S)-3-amino pentanoyl-N-[[3-(aminosulfonyl)-5-chlorophenyl]sulfonyl]glycinamide

- 40 Step (A44a) Following a procedure analogous to Step (A4a), compound **27b** (Scheme 4) was coupled with 3-(aminosulfonyl)-

5 5-chlorophenyl sulfonamide to provide the title compound.
MS found (M-1)⁻ 924.4.

Example A45

10 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-amino pentanoyl-N-[[3,5-
bis(trifluoromethyl)phenyl]sulfonyl]glycinamide

Step (A45a) Following a procedure analogous to Step (A4a),
compound **27b** (Scheme 4) was coupled with 3,5-
15 bis(trifluoromethyl)phenyl sulfonamide to provide the title
compound. MS found (M+1)⁺ 949.4.

Example A46

20 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[4-[5-[3-(4-
chlorophenyl)-3-oxo-1-propenyl]-2-
furanyl]phenyl]sulfonyl]glycinamide

Step (A46a): Following a procedure analogous to step (A4a),
25 compound **27b** (Scheme 4) was coupled with 4-[5-[3-(4-
chlorophenyl)-3-oxo-1-propenyl]-2-furanyl]phenyl
sulfonamide providing the title compound. MS found (M+1)⁺
1043.5.

Example A47

30 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-
L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-
[[(phenylmethyl) amino] carbonyl] phenyl] sulfonyl] glycinamide

35 Step (A47a): Following a procedure analogous to step (A4a),
27b (Scheme 4) was coupled with 3-[(phenylmethyl) amino]-
carbonyl] phenyl] sulfonamide providing the title product as
crystalline solid. MS found (M+1)⁺ 946.6.

5

Example A48

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[(2,2,2-trifluoroethyl)amino]carbonyl]phenyl]sulfonyl]glycinamide

10 Step (A48a): Following a procedure analogous to step (A4a), **27b** (Scheme 4) was coupled with 3-[(2,2,2-trifluoroethyl)amino]carbonyl]phenyl]sulfonamide providing the title product as crystalline solid. MS found (M+1)⁺ 938.5.

15

Example A49

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-2-oxo-(3S)-3-aminopentanoyl-N-[[3-[(benzoylamino)sulfonyl]-5-chlorophenyl]sulfonyl]glycinamide

20

Step (A49a): Following a procedure analogous to step (A4a), **27b** (Scheme 4) was coupled with 3-[(benzoylamino)sulfonyl]-5-chlorophenyl]-sulfonamide providing the title product as crystalline solid. MS found (M+1)⁺ 1030.6.

25

Example A50

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoylglycine

30

Step (A50a): To a suspension of KOtBu (3.55g, 31.7mmol) in 15mL CH₂Cl₂ was added N-CBZ-phosphonolycine trimethyl ester (9.46g, 28.5mmol) at -78°C under N₂. This mixture was stirred for 15min at this temperature and 2,2-difluoroacetaldehyde ethyl hemiacetal (4.0g, 31.7mmol) was added slowly. The resulted mixture was warmed up to room temperature and stirred overnight. Most solvent was removed and the residue was dissolved in ethyl acetate. The mixture was washed with cold water, dried over magnesium sulfate and concentrated. Flash chromatography (10-15% EtOAc/Hexane) gave the desired alkene (1.97g, 24%) (Scheme

40

5 3, **11**) as a clear oil (4:1 mixture of Z:E isomers).
(M+1)⁺ 286.3.

Step (A50b): A mixture the material from Step (A50a)
(0.90g, 3.16mmol) and of (+)-1,2-bis((2S,5S)-2,5-diethyl-
10 phospholano)benzene-(cyclooctadiene)rhodium(I)
trifluoromethanesulfonate ([Rh(COD)(S,S-di-Ethyl-
DUPHOS)]⁺CF₃SO₃⁻) (25mg, 0.03mmol, 1 mol%) in 20mL MeOH
was hydrogenated at 50psi for 15h. After evaporation of
solvent, the residue was dissolved in 30% EtOAc/Hexane and
15 the solution was passed through a pad of silica gel to
remove trace amount of the catalyst. Evaporation of
solvent yielded the desired compound (Scheme 3, **12**) as a
crystalline solid (0.91g, 100%).

20 Step (A50c): To a solution of the material from Step
(A50b) (1.95g, 5.23mmol) in 50mL CH₂Cl₂ under N₂ was added
dropwise 5.49mL DIBAL (1.0M solution in CH₂Cl₂, 5.49mmol)
at -78°C over 15min. After stirring at this temperature
for 2h, the mixture was quenched with 10mL 5% potassium
25 hydrogen sulfate solution. Then the mixture was warmed up
to room temperature, diluted with CH₂Cl₂, washed with
KHSO₄, NaHCO₃ and brine, dried over NaSO₄ and concentrated.
Flash chromatography (15-30% EtOAc/Hexane) afforded 1.20g
(89%) of the desired aldehyde (Scheme 3, **13**) as a white
30 solid.

Step (A50d): Butyl lithium (2.5M solution in hexane, 4.1mL,
10.3mmol) was added dropwise to a solution of
tris(methylthio)methane (1.58g, 10.3mmol) in 20mL THF at
35 -64°C and the mixture was stirred at this temperature for
20min. Then a solution of 0.66g (2.57mmol) of the
material from Step (A50c) in 5.0mL THF was added dropwise to
the above mixture over 10min. The resulting mixture was
stirred at -30°C and warmed up to room temperature. Then
40 the reaction mixture was quenched with saturated NH₄Cl, and
diluted with ethyl acetate. The organic phase was

5 separated and washed with 5% KHSO₄, H₂O, NaHCO₃, brine,
dried over NaSO₄ and concentrated. Flash chromatography
(10-15% EtOAc/Hexane) yielded 0.90g (85%) of the desired
product (Scheme 3, **14**) as a clear oil (a mixture of two
diasteromers).

10

Step (A50e): To a solution of 0.15g (0.36mmol) of the
material from Step (A50d) in a mixed solvent of MeOH/H₂O
(12mL/1.0mL) were added 0.46g (1.69mmol) mercury(II)
chloride and 0.12g (0.58mmol) mercury(II) oxide. The
15 resulted suspension was stirred at room temperature for 2h.
Then the reaction mixture was filtered through a pad of
Celite and most of the solvent was removed. The residue
was dissolved in ethyl acetate, and this mixture was washed
20 with 70% ammonium acetate, saturated ammonium chloride,
sodium bicarbonate and dilute NaCl solution, dried over
magnesium sulfate and concentrated. Chromatography (30%
EtOAc/Hexane) gave 0.11g (96%) of the desired product
(Scheme 3, **15**) as a clear oil (a mixture of two
diasteromers).

25

Step (A50f): Following a procedure analogous to Step
(A1d), the material from Step (A50e) was hydrogenated to
afford the desired α -hydroxyl β -amino ester (Scheme 3, **16**)
as a crystalline solid.

30

Step (A50g): Following a procedure analogous to Step (A1j),
the material from Step (A50f) was coupled with compound **24**
(Scheme 4) to give the α -hydroxyester (Scheme 4, **25a**) as a
crystalline solid.

35

Step (A50h): Following a procedure analogous to Step
(A2e), the material from Step (A50g) was converted to the
desired α -hydroxyacid.

40

Step (A50i): Following a procedure analogous to Step
(A1i), the above acid from Step (A50h) was coupled with

5 Gly-OtBu to afford the desired product (Scheme 4, **25b**) as a crystalline solid.

Step (A50j): Following a procedure analogous to Step (A1k), the material from Step (A50i) was oxidized to α -
10 ketoamide (Scheme 4, **26b**) as crystalline solid.

Step (A50k): Following a procedure analogous to Step (A1l), the material from Step (A50j) was treated with TFA to afford the title compound (Scheme 4, **27b**) as a white
15 solid. MS found (M+1)⁺ 710.4.

Example A51

(3S)-5,5-difluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N-(2H-tetrazol-5-ylmethyl)pentanamide
20

Step (A51a): Following a procedure analogous to Steps (A1f) and (A1g), the material from Step (A50h) was coupled with aminomethyltetrazole to afford the title product as
25 acrySTALLINE solid. MS found (M+1)⁺ 734.4.

Example A52

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide
30

Step (A52a) Following a procedure analogous to Step (A4a), the material from Step (A50k) was coupled with 3,5-dichlorophenyl-sulfonamide to give the title product. MS
35 found (M+1)⁺ 918.9.

Example A53

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide
40

5 Step (A53a) Following a procedure analogous to Step (A4a), the material from Step (A50k) was coupled with 2-chlorophenylsulfonamide to give the title product. MS found (M+1)⁺ 883.3.

10

Example A54

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide

15 Following a procedure analogous to Step (A4a), the material from Step (A50k) was coupled with [5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonamide to give the title product. MS found (M+1)⁺ 914.5.

20

Example A55

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-(3-aminosulfonyl-5-chlorophenyl)sulfonyl]glycinamide

25 Step (A55a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3-aminosulfonyl-5-chlorophenyl]sulfonamide to give the title product. MS found (M+1)⁺ 962.4.

30

Example A56

(3S)-5,5,5-trifluoro-2-oxo-3-[[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexyl-L-alanyl]amino]-N-(2H-tetrazol-5-ylmethyl)pentanamide

35 Step (A56a): Following a procedure analogous to Steps (A1a-d), 2-hydroxyl-3-amino-5-trifluorovaleric acid methylester (Scheme 1, **5** where R₁=H, R₂=CH₂CF₃, W''=OMe) was obtained.
(A56b): Following a procedure analogous to Step (A1j), the product from (A56a) was coupled with the product from (A1I)
40 to give the desired product (Scheme 4, **25a**).

5 (A56c): Following a procedure analogous to Steps (A2e-g),
the material from Step (A56b) was converted to the desired
product as a white solid (Scheme 6). MS found: (M+1)+
752.9.

10 Example A57

N-[4-*sec*-butyl-15-[[[3-chloro-5-[[3,3,3-
trifluoropropanoyl)amino]sulfonyl]phenyl)sulfonyl]amino]-7-
(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-
15 pyrazinecarboxamide

Step (A57a): Following a procedure analogous to step (A4a),
the material from step (A50k) was coupled with (3-chloro-5-
[[3,3,3-trifluoropropanoyl)amino]sulfonamide to give the
20 title product. MS found (M+1)⁺ 1073.4.

Example A58

N-[4-*sec*-butyl-15-[(3-chloro-5-
[(hexanoylamino)sulfonyl]phenyl)sulfonyl]amino]-7-
25 (cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-
pyrazinecarboxamide

Step (A58a): Following a procedure analogous to step (A4a),
30 the material from step (A50k) was coupled with (3-chloro-
5-[(hexanoylamino)sulfonamide to give the title product. MS
found (M+1)⁺ 1061.3.

Example A59

35 *N*-[15-[[[1,1'-biphenyl]-3-ylsulfonyl]amino]-4-*sec*-butyl-7-
(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-
hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-
pyrazinecarboxamide

40 Step (A59a): Following a procedure analogous to step (A4a),
the material from step (A50k) was coupled with ([1,1'-

5 biphenyl]-3-yl] sulfonamide to give the title product. MS
found (M+1)⁺ 890.4.

Example A60

10 N-(4-sec-butyl-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-15-
{[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]amino}-
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-
pyrazinecarboxamide

15 Step (A60a): Following a procedure analogous to step (A4a),
the material from step (A50k) was coupled with [(4'-
methoxy[1,1'-biphenyl]-4-yl) sulfonamide to give the title
product. MS found (M+1)⁺ 920.1.

Example A61

20 N-(4-sec-butyl-7-(cyclohexylmethyl)-15-{[(3',5'-
dichloro[1,1'-biphenyl]-4-yl)sulfonyl]amino}-10-ethyl-1-
isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-
1-yl)-2-pyrazinecarboxamide

25 Step (A61a): Following a procedure analogous to step (A4a),
the material from step (A50k) was coupled with [(3',5'-
dichloro[1,1'-biphenyl]-4-yl)sulfonamide to give the title
product. MS found (M+1)⁺ 958.5.

Example A62

30 N-[4-sec-butyl-15-{[(4'-chloro[1,1'-biphenyl]-3-
yl)sulfonyl]amino}-7-(cyclohexylmethyl)-10-(2,2-
difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-
tetraazapentadec-1-yl]-2-pyrazinecarboxamide

35 Step (A62a): Following a procedure analogous to step (A4a),
the material from step (A50k) was coupled with [(4'-
chloro[1,1'-biphenyl]-3-yl)sulfonamide to give the title
product. MS found (M+1)⁺ 960.6.

5

Example A63

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-({[3-(2-methylphenoxy)phenyl]sulfonyl}amino)-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

10

Step (A63a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3-(2-methylphenoxy)phenyl]sulfonamide to give the title product. MS found (M+1)⁺ 956.2.

15

Example A64

N-[4-*sec*-butyl-15-({[3-(2-chlorophenoxy)phenyl]sulfonyl}amino)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

20

Step (A64a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3-(2-chlorophenoxy)phenyl]phenyl]sulfonamide to give the title product. MS found (M+1)⁺ 976.3.

25

Example A65

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid

30

Step (A65a): Following a procedure analogous to step (A4), the material from step (A50k) was treated with Dess-Martin reagent to obtain the title product. MS found (M+1)⁺ 653.5.

35

Example A66

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-({[4'-methyl[1,1'-biphenyl]-3-yl]sulfonyl}amino)-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide

40

5

Step (A66a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [(4'-methyl[1,1'-biphenyl]-3-yl)sulfonamide to give the title product. MS found (M+1)⁺ 940.1.

10

Example A67

N-[15-({[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl)sulfonyl}amino)-4-sec-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-
15 3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A67a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with [3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl)sulfonamide to
20 give the title product. MS found (M+1)⁺ 1061.8.

Example A68

N-[4-sec-butyl-15-[(5-[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-
25 (2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A68a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with {(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to
30 give the title product. MS found (M+1)⁺ 1001.9.

Example A69

N-[4-sec-butyl-15-[(5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-
35 (2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A69a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with {5-[(2-

40

5 chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to
give the title product. MS found (M+1)⁺ 1011.2.

Example A70

10 N-{4-sec-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-
1-isobutyl-15-[(5-[(4-methoxybenzoyl)amino]-1,3,4-
thiadiazol-2-yl)sulfonyl)amino]-2,5,8,11,12,15-hexaoxo-
3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

15 Step (A70a): Following a procedure analogous to step (A4a),
the material from step (A50k) was coupled with {5-[(4-
methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to
give the title product. MS found (M+1)⁺ 1006.8.

Example A71

20 N-{4-sec-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-
1-isobutyl-15-[(5-[(3-methoxybenzoyl)amino]-1,3,4-
thiadiazol-2-yl)sulfonyl)amino]-2,5,8,11,12,15-hexaoxo-
3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

25 Step (A71a): Following a procedure analogous to step (A4a),
the material from step (A50k) was coupled with {5-[(3-
methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to
give the title product. MS found (M+1)⁺ 1007.1.

Example A72

30 N-{4-sec-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-
15-[(5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-
yl)sulfonyl)amino]-1-isobutyl-2,5,8,11,12,15-hexaoxo-
3,6,9,13-tetraazapentadec-1-yl}-2-pyrazinecarboxamide

35 Step (A72a): Following a procedure analogous to step (A4a),
the material from step (A50k) was coupled with {5-[(3,5-
dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl}sulfonamide to
give the title product. MS found (M+1)⁺ 1007.1.

5

Example A73

N-(4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-15-[(3-phenoxyphenyl)sulfonyl]amino)-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide

10

Step (A73a): Following a procedure analogous to step (A4a), the material from step (A50k) was coupled with (3-phenoxyphenyl)sulfonamide to give the title product. MS found (M+1)⁺ 941.8.

15

Example A74

6-*sec*-butyl-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-1,4,7,10,13-pentaoxo-1-(2-pyrazinyl)-2,5,8,11-tetraazatetradecan-14-oic acid

20

Step (A74a): Following a procedure analogous to step (A65a), the material from step (A50k) was treated with Dess-Martin reagent to give the title product. MS found (M+1)⁺ 617.4.

25

Example A75

N-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-15-[(5-[(3-methylbutanoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino}-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl)-2-pyrazinecarboxamide

30

Step (A75a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)⁺ 957.0.

35

Example A76

N-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[(5-(hexanoylamino)-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

5 Step (A76a): Following a procedure analogous to step (A4a),
the title compound was obtained. MS found (M+1)⁺ 971.0.

Example A77

10 Methyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-(2,2-
difluoroethyl)-3-isobutyl-6-[(1*R*)-1-methylpropyl]-
1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-
pentaazaheptadecan-17-oate

15 Step (A77a): Following a procedure analogous to step (A4a),
the title compound was obtained. MS found (M+1)⁺ 724.4.

Example A78

20 *N*-[4-*sec*-butyl-15-{{(3-chloro-5-{{(3-
chlorobenzoyl)amino}sulfonyl}phenyl)sulfonyl}amino}-7-
(cyclohexylmethyl)-10-ethyl-1-isobutyl-2,5,8,11,12,15-
hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-
pyrazinecarboxamide

25 Step (A78a): Following a procedure analogous to step (A4a),
the title compound was obtained. MS found (M+1)⁺ 1066.1.

Example A79

30 *N*-[4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-
1-isobutyl-2,5,8,11,12,15-hexaoxo-15-{{[4'-
(trifluoromethyl)[1,1'-biphenyl]-3-yl}sulfonyl}amino)-
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A79a): Following a procedure analogous to step (A4a),
35 the title compound was obtained. MS found (M+1)⁺ 993.9.

Example A80

40 *N*-[15-[[[1,1'-biphenyl]-3-ylsulfonyl]amino]-4-*sec*-butyl-7-
(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-
pyrazinecarboxamide

5

Step (A80a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)⁺ 926.1.

Example A81

10 *N*-[4-*sec*-butyl-15-[(5-[(4-*tert*-butylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl)amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

15 Step (A81a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)⁺ 1033.1.

Example A82

20 *N*-[4-*sec*-butyl-15-[(3-chloro-5-[(3-methylbutanoyl)amino]sulfonyl)phenyl)sulfonyl]amino]-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

25 Step (A82a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)⁺ 1047.7.

Example A83

30 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-1-isobutyl-14-[4-(4-methoxyphenyl)-5-(trifluoromethyl)-4*H*-1,2,4-triazol-3-yl]-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide

35 Step (A83a): Following a procedure analogous to step (A4a), the title compound was obtained. MS found (M+1)⁺ 907.8.

Example A84

40 *N*-{4-*sec*-butyl-7-(cyclohexylmethyl)-10-(2,2-difluoroethyl)-15-[(5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-

5 yl)sulfonyl)amino]-1-isobutyl-2,5,8,11,12,15-hexaoxo-
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A84a): Following a procedure analogous to step (A4a),
the title compound was obtained. MS found (M+1)⁺ 1005.2.

10

Example A85

N-[4-sec-butyl-15-[(5-[(4-chlorobenzoyl)amino]-1,3,4-
thiadiazol-2-yl)sulfonyl)amino]-7-(cyclohexylmethyl)-10-
(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-
15 3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide

Step (A85a): Following a procedure analogous to step (A4a),
the title compound was obtained. MS found (M+1)⁺ 1011.5.

20

Example A86

N-[4-sec-butyl-7-(cyclohexylmethyl)-15-[(5-[(3,5-
difluorobenzoyl)amino]-1,3,4-thiadiazol-2-
yl)sulfonyl)amino]-10-(2,2-difluoroethyl)-1-isobutyl-
2,5,8,11,12,15-hexaoxo-3,6,9,13-tetraazapentadec-1-yl]-2-
25 pyrazinecarboxamide

Step (A86a): Following a procedure analogous to step (A4a),
the title compound was obtained. MS found (M+1)⁺ 1013.1.

30

Example A87

N-[4-sec-butyl-15-[(5-[(3-chlorobenzoyl)amino]-1,3,4-
thiadiazol-2-yl)sulfonyl)amino]-7-(cyclohexylmethyl)-10-
(2,2-difluoroethyl)-1-isobutyl-2,5,8,11,12,15-hexaoxo-
3,6,9,13-tetraazapentadec-1-yl]-2-pyrazinecarboxamide
35

Step (A87a): Following a procedure analogous to step (A4a),
the title compound was obtained. MS found (M+1)⁺ 1011.3.

5

Example A88

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl}-2-pyrazinecarboxamide

10 Step (A88a): Following a procedure analogous to steps (A1) and (A4a). The detailed procedure can be found in Han, W. et.; *Bioorg. Med. Chem. Lett.* 10, 711-713, 2000 and is hereby incorporated by reference in its entirety. The title compound was obtained. MS found (M+1)⁺ 656.4.

15

Example A89

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-yn-1-yl}-2-pyrazinecarboxamide

20

Step (A89a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found (M+1)⁺ 654.5.

25

Example A90

tert-butyl (3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-oate

30

Step (A90a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found (M+1)⁺ 730.5.

35

Example A91

N-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-pentaoxo-14-phenyl-3,6,9,13-tetraazatetradec-1-yl}-2-pyrazinecarboxamide

5 Step (A91a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found (M+1)⁺ 706.4.

Example A92

10 *N*-((1*S*)-1-{[(1*S*,2*R*)-1-{[(1*S*)-1-(cyclohexylmethyl)-2-
{[(1*S*)-1-ethyl-2,3-dioxo-3-(1-pyrrolidinyl)propyl]amino}-2-
oxoethyl)amino]carbonyl}-2-methylbutyl)amino]carbonyl}-3-
methylbutyl)-2-pyrazinecarboxamide

15 Step (A92a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found (M+1)⁺ 670.3

Example A93

20 *N*-{(1*S*,4*S*,7*S*,10*S*)-7-(cyclohexylmethyl)-10-ethyl-15,15,15-
trifluoro-1-isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12-
penta-3,6,9,13-tetraazapentadec-1-yl}-2-
pyrazinecarboxamide

25 Step (A93a): Following a procedure analogous to step (A88a), the title compound was obtained. MS found (M+1)⁺ 698.2.

Example A94

30 *N*-{(1*S*,4*S*,7*S*,10*S*)-15-amino-7-(cyclohexylmethyl)-10-ethyl-1-
isobutyl-4-[(1*R*)-1-methylpropyl]-2,5,8,11,12,15-hexa-3,6,9,13-
tetraazapentadec-1-yl}-2-pyrazinecarboxamide

Step (A94a): Following a procedure analogous to step
35 (A88a), the title compound was obtained. MS found (M+1)⁺ 673.4.

Example A95

40 (3*S*,6*S*,9*S*,12*S*,16*S*)-9-(cyclohexylmethyl)-12-ethyl-3-
isobutyl-16-methyl-6-[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-

5 hexaoxo-1-(2-pyrazinyl)-2,5,8,11,15-pentaazaheptadecan-17-
oic acid

Step (A95a): Following a procedure analogous to step
(A88a), the title compound was obtained. MS found (M+1)⁺
10 688.5.

Example A96

N-[9-*sec*-butyl-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-
2,5,8,11,14-pentaoxo-14-(2-pyrazinyl)-4,7,10,13-
15 tetraazatetradec-1-anoyl]aspartic acid

Step (A96a): Following a procedure analogous to step
(A88a), the title compound was obtained. MS found (M+1)⁺
20 732.4.

Example A97

(3*S*,6*S*,9*S*,12*S*)-9-(cyclohexylmethyl)-12-ethyl-3-isobutyl-6-
[(1*R*)-1-methylpropyl]-1,4,7,10,13,14-hexaoxo-1-(2-
25 pyrazinyl)-2,5,8,11,15-pentaazaoctadecan-18-oic acid

Step (A97a): Following a procedure analogous to step
(A88a), the title compound was obtained. MS found (M+1)⁺
30 688.5.

Example B1

1,1-dimethylethyl *N*-(2-pyrazinylcarbonyl)-*L*-leucyl-*L*-
isoleucyl-(4*R*)-4-(phenylmethoxy)-*L*-prolyl-5,5-difluoro-2-
35 oxo-(3*S*)-3-aminopentanoylglycine

Step (B1a): Following a procedure analogous to step (A1)
and (A50), the compound **32a** {Pz(CO)-Lue-Ile-Hyp(OBn)-
NHCH(CH₂CHF₂)CH(OH)CO₂Me} was obtained as crystalline
solid. MS found (M+1)⁺ 719.1.

40 Step (B1b): Following a procedure analogous to step (A2e),
the product from step (B1a) was treated with LiOH to

5 provide the corresponding α -hydroxyacid as crystalline solid. MS found (M+1)⁺ 715.1; (M-1)⁻ 713.

Step (B1c): Following a procedure analogous to step (A1j) and step (A1k), the above material was coupled with Gly-
10 OtBu followed by oxidation to provide the title product (Scheme 5, **33**) as crystalline solid. MS found (M+1)⁺ 816.4.

Example B2

15 N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-di fluoro-2-oxo-(3S)-3-aminopentanoylglycine

Step (B2a): Following a procedure analogous to Step (A11),
20 the material from Step (B1c) was treated with TFA to afford title product (Scheme 5, **34**) as a white solid. MS found (M+1)⁺ 760.3.

Example B3

25 (4R)-1-[N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl]-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H)-tetrazol-5-yl methyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide

Step (B3a): Following a procedure analogous to Steps (A2f-
30 g), the material from Step (B1b) was coupled with aminotetrazole followed by oxidation to give the title product as a white solid. MS found (M+1)⁺ 784.4.

Example B4

35 (4R)-N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-3-methoxy-2,3-dioxopropyl]-4-(phenylmethoxy)-L-prolinamide

Step (B4a): Following a procedure analogous to step (A2g),
40 the material from (B1a) was oxidized to the desired product. MS found (M+1)⁺ 717.3.

5

Example B5

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(3-chlorophenyl)sulfonyl]glycinamide

10

Step (B5a): Following a procedure analogous to Step (A4a), the material from Step (B2a) was coupled with 3-chlorophenylsulfonamide to afford the title product as a white solid. MS found (M+1)⁺ 933.3.

15

Example B6

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-carboxy-2-chlorophenyl)sulfonyl]glycinamide

20

Step (B6a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with 5-carboxy-2-chlorophenylsulfonamide to afford title product as white solid. MS found (M+1)⁺ 978.2

25

Example B7

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[(5-acetylamino)1,3,4-thiadiazol-2-yl)sulfonyl]glycinamide

30

Step (B7a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with N-[(5-acetylamino)1,3,4-thiadiazol-2-yl)sulfonamide to afford title product as white solid. MS found (M+1+H₂O)⁺ 982.5.

35

Example B8

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl-N-[3,5-dichlorophenyl)sulfonyl]glycinamide

40

5

Step (B8a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3,5-dichlorophenyl) sulfonamide to afford title product as white solid. MS found (M+1)⁺ 967.6.

10

Example B9

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-(4-methyl-3-nitrophenyl)sulfonyl]-glycinamide

15

Step (B9a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (4-methyl-3-nitrophenyl) sulfonamide to afford title product as white solid. MS found (M+1)⁺ 958.4.

20

Example B10

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-(3-carboxyl-4-chloro-2-fluorophenyl)sulfonyl]-glycinamide

25

Step (B10a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3-carboxyl-4-chloro-2-fluorophenyl)sulfonamide to afford title product as white solid. MS found (M+1)⁺ 995.4.

30

Example B11

N-(2-pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-(4R)-4-(phenylmethoxy)-L-prolyl-5,5-difluoro-2-oxo-(3S)-3-aminopentanoyl N-[(3-chloro-4-acetylamino)phenyl]sulfonyl]-glycinamide

35

Step (B11a): Following a procedure analogous to step (4a), the material from step (B2a) was coupled with (3-chloro-4-

40

5 acetylamino)phenyl sulfonamide to afford title product as
white solid. MS found (M+1)⁺ 1116.5.

Example B12

10 N-((1S)-1-[[[(1S,2R)-1-[[(2S,4R)-2-([[(1S)-3-({2-[(3-
[(benzoylamino)sulfonyl]-5-chlorophenyl)sulfonyl)amino]-2-
oxoethyl)amino)-1-(2,2-difluoroethyl)-2,3-
dioxopropyl]amino}carbonyl)-4-
(benzyloxy)pyrrolidinyl]carbonyl]-2-
methylbutyl)amino]carbonyl]-3-methylbutyl)-2-
15 pyrazinecarboxamide

Step (B12a): Following a procedure analogous to step (B7a),
the title compound was obtained. MS found (M+1)⁺ 1117.4.

Example B13

20 tert-butyl ({(3S)-3-[[[(2S,4R)-4-(benzyloxy)-1-[(2S)-3-
methyl-2-([[(2S)-3-methyl-2-[(2-
pyrazinylcarbonyl)amino]butanoyl]amino)butanoyl]pyrrolidiny
l]carbonyl)amino]-5,5-difluoro-2-oxopentanoyl]amino)acetate
25

Step (B13a): Following a procedure analogous to step (B7a),
the title compound was obtained. MS found (M+1)⁺ 788.9.

Example B14

30 N-((1S)-1-[[[(1S,2R)-1-[[(2S,4R)-4-(benzyloxy)-2-([[(1S)-3-
[(2-[(3-chloro-4-methylphenyl)sulfonyl]amino)-2-
oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-
dioxopropyl]amino}carbonyl)pyrrolidinyl]carbonyl]-2-
methylbutyl)amino]carbonyl]-3-methylbutyl)-2-
35 pyrazinecarboxamide

Step (B14a): Following a procedure analogous to step (B7a),
the title compound was obtained. MS found (M+1)⁺ 948.3.

5

Example B15

$N-((1S)-1-{\{[(1S,2R)-1-{\{(2S,4R)-4-(benzyloxy)-2-{\{[(1S)-3-\\$
 $(\{2-[(\{5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-\\$
 $yl\}sulfonyl)amino]-2-oxoethyl\}amino)-1-(2,2-difluoroethyl)-\\$
 $2,3-dioxopropyl\}amino\}carbonyl)pyrrolidinyl\}carbonyl\}-2-\\$
 10 methylbutyl)amino\}carbonyl\}-3-methylbutyl)-2-
 pyrazinecarboxamide

Step (B15a): Following a procedure analogous to step (B7a),
 the title compound was obtained. MS found $(M+1)^+$ 1061.3.

15

Example B16

Methyl $(\{(3S)-3-[(\{(2S,4R)-4-(benzyloxy)-1-[(2S,3R)-3-\\$
 $methyl-2-[(2S)-4-methyl-2-[(2-\\$
 20 pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]pyrrolidi
 $nyl\}carbonyl)amino]-5,5-difluoro-2-\\$
 $oxopentanoyl\}amino)acetate$

Step (B16a): Following a procedure analogous to step (B7a),
 the title compound was obtained. MS found $(M+1)^+$ 774.6.

25

Example B17

$N-((1S)-1-{\{[(1S,2R)-1-{\{(2S,4R)-4-(benzyloxy)-2-{\{[(1S)-3-\\$
 $[(2-[(2,4-dichloro-5-methylphenyl)sulfonyl]amino\}-2-\\$
 $oxoethyl)amino]-1-(2,2-difluoroethyl)-2,3-\\$
 30 dioxopropyl\}amino\}carbonyl)pyrrolidinyl\}carbonyl\}-2-
 $methylbutyl)amino\}carbonyl\}-3-methylbutyl)-2-\\$
 pyrazinecarboxamide

Step (B17a): Following a procedure analogous to step (B7a),
 35 the title compound was obtained. MS found $(M+1)^+$ 982.6.

Example B18

$N-[(1S)-1-(\{[(1S,2R)-1-(\{(2S,4R)-4-(benzyloxy)-2-[(\{(1S)-1-\\$
 $(2,2-difluoroethyl)-3-[(2-[(3,4-\\$
 40 difluorophenyl)sulfonyl]amino\}-2-oxoethyl)amino]-2,3-
 $dioxopropyl\}amino)carbonyl]pyrrolidinyl\}carbonyl)-2-$

5 methylbutyl]amino}carbonyl)-3-methylbutyl]-2-
pyrazinecarboxamide

Step (B18a): Following a procedure analogous to step (B7a),
the title compound was obtained. MS found (M+1)⁺ 935.7.

10

Example B19

Methyl 5-({[({(3*S*)-3-[({(2*S*,4*R*)-4-(benzyloxy)-1-[(2*S*,3*R*)-3-
methyl-2-({(2*S*)-4-methyl-2-[(2-
pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]pyrrolidi
15 nyl}carbonyl)amino]-5,5-difluoro-2-
oxopentanoyl}amino)acetyl]amino)sulfonyl)-2,4-
dichlorobenzoate

Step (B19a): Following a procedure analogous to step (B7a),
20 the title compound was obtained. MS found (M+1)⁺ 1026.7.

Example B20

N-{(1*S*)-1-[({(1*S*,2*R*)-1-[({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-
(2,2-difluoroethyl)-3-{[2-({[4-(3,5-dimethyl-1-
25 piperidiny]l)-3-nitrophenyl]sulfonyl}amino)-2-
oxoethyl]amino}-2,3-
dioxopropyl)amino]carbonyl]pyrrolidinyl)carbonyl]-2-
methylbutyl}amino)carbonyl]-3-methylbutyl}-2-
pyrazinecarboxamide

30

Step (B20a): Following a procedure analogous to step (B7a),
the title compound was obtained. MS found (M+1)⁺ 1056.0.

Example B21

35 *N*-[(1*S*)-1-({[(1*S*,2*R*)-1-({(2*S*,4*R*)-4-(benzyloxy)-2-[({(1*S*)-1-
(2,2-difluoroethyl)-3-[(2-({[3-nitrophenyl]sulfonyl]amino}-
2-oxoethyl)amino]-2,3-
dioxopropyl}amino)carbonyl]pyrrolidinyl)carbonyl)-2-
methylbutyl]amino)carbonyl)-3-methylbutyl]-2-
40 pyrazinecarboxamide

5 Step (B21a): Following a procedure analogous to step (B7a),
the title compound was obtained. MS found (M+1)⁺ 944.8.

Example B22

10 N-((1S)-1-(((1S,2R)-1-((2S,4R)-4-(benzyloxy)-2-(((1S)-1-(
(2,2-difluoroethyl)-3-([2-([5-(hexanoylamino)-1,3,4-
thiadiazol-2-yl]sulfonyl)amino)-2-oxoethyl]amino)-2,3-
dioxopropyl)amino]carbonyl]pyrrolidinyl)carbonyl]-2-
methylbutyl)amino)carbonyl]-3-methylbutyl)-2-
pyrazinecarboxamide

15

Step (B22a): Following a procedure analogous to step (B7a),
the title compound was obtained. MS found (M+1)⁺ 1021.1.

Example B23

20 5-((((3S)-3-(((2S,4R)-4-(benzyloxy)-1-((2S,3R)-3-methyl-
2-((2S)-4-methyl-2-((2-
pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]pyrrolidi
nyl)carbonyl)amino]-5,5-difluoro-2-
oxopentanoyl)amino)acetyl)amino)sulfonyl)-2,4-
25 dichlorobenzoic acid

Step (B23a): Following a procedure analogous to step (B7a),
the title compound was obtained. MS found (M+1)⁺ 1012.6.

30

Example C1

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoylglycine

35 Step (C1a): Following the procedures analogous to step (A1)
and step (A2), the title product was obtained as
crystalline solid. MS found (M+1)⁺ 659.4.

Example C2

40 N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-3-
cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-
[(trifluoromethyl)sulfonyl]glycinamide

5

Step (C2a): Following a procedure analogous to step (A4a), the material from step (C1a) was coupled with trifluoromethylsulfonamide to afford the title product as crystalline solid. MS found (M+1)⁺ 790.3.

10

Example C3

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3,5-dichlorophenyl)sulfonyl]glycinamide

15

Step (C3a): Following the procedures analogous to step (A4a), the material from step (C1a) was coupled with 3,5-dichlorophenyl)sulfonamide to afford the title product as crystalline solid. MS found (M+1)⁺ 866.6.

20

Example C4

N-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-Lisoleucyl-3-cyclohexylalanyl-2-oxo-3-aminopentanoyl-N-[(3-nitrophenyl)sulfonyl]glycinamide

25

Step (C4a): Following the procedures analogous to step (A4a), the material from step (C1a) was coupled with -(3-nitrophenyl)sulfonamide to afford the title product as crystalline solid. MS found (M+1)⁺ 841.3.

30

Example C5

(4R)-1-[[5-(4-chlorophenyl)-2-furanyl]carbonyl]-L-isoleucyl-N-[(1S)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2H-tetrazol-5-ylmethyl)amino]propyl]-4-(phenylmethoxy)-L-prolinamide

35

Step (C5a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)⁺ 769.3.

5

Example C6

(2*S*,4*R*)-4-(benzyloxy)-*N*-{(1*S*)-1-(2,2-difluoroethyl)-2,3-dioxo-3-[(2*H*-tetraazol-5-ylmethyl)amino]propyl}-1-((2*S*,3*R*)-3-methyl-2-[[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

10

Step (C6a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)⁺ 771.5.

15

Example C7

tert-butyl {[(3*S*)-3-([(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-[[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl]amino)-5,5-difluoro-2-oxopentanoyl]amino}acetate

20

Step (C7a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)⁺ 803.4.

25

Example C8

[(3*S*)-3-([(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-[[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)pyrrolidinyl]carbonyl]amino)-5,5-difluoro-2-oxopentanoyl]amino}acetic acid

30

Step (C8a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)⁺ 747.3.

35

Example C9

(2*S*,4*R*)-*N*-[(1*S*)-3-{[2-([5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]amino)-2-oxoethyl]amino}-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-3-methyl-2-[[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

40

5 Step (C9a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)⁺ 951.2.

Example C10

10 (2*S*,4*R*)-4-(benzyloxy)-*N*-((1*S*)-1-(2,2-difluoroethyl)-3-([2-([5-(hexanoylamino)-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-2-oxoethyl]amino)-2,3-dioxopropyl)-1-((2*S*,3*R*)-3-methyl-2-
25 {[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

15

Step (C10a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as crystalline solid. MS found (M+1)⁺ 1007.9.

Example C11

20

((2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-([5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-2-oxoethyl]amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-
25 {[(2*S*,3*R*)-3-methyl-2-[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

25

Step (C11a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as

30 crystalline solid. MS found (M+1)⁺ 1048.3.

Example C12

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-1-(2,2-difluoroethyl)-3-({2-
35 {[(5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl]amino)-2-oxoethyl]amino)-2,3-dioxopropyl]-1-
{[(2*S*,3*R*)-3-methyl-2-[(9-oxo-9*H*-fluoren-1-yl)carbonyl]amino}pentanoyl)-2-pyrrolidinecarboxamide

Step (C12a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained as
40 crystalline solid. MS found (M+1)⁺ 1041.8.

5

Example C13

tert-butyl {[(3*S*)-3-({ [(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-
 10 {[5-(4-chlorophenyl)-2-furoyl]amino}-3-
 methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-
 2-oxopentanoyl]amino}acetate

Step (C13a): Following the procedures analogous to steps
 (A50) and (B1), the title compound was obtained. MS found
 (M+1)⁺ 801.9.

15

Example C14

{[(3*S*)-3-({ [(2*S*,4*R*)-4-(benzyloxy)-1-((2*S*,3*R*)-2-
 chlorophenyl)-2-furoyl]amino}-3-
 methylpentanoyl)pyrrolidinyl]carbonyl}amino)-5,5-difluoro-
 20 2-oxopentanoyl]amino}acetic acid

25

Step (C14a): Following the procedures analogous to steps
 (A50) and (B1), the title compound was obtained. MS found
 (M+1)⁺ 746.0.

Example C15

(2*S*,4*R*)-*N*-[(1*S*)-3-{[2-({[5-(acetylamino)-1,3,4-thiadiazol-
 2-yl]sulfonyl}amino)-2-oxoethyl]amino}-1-(2,2-
 30 difluoroethyl)-2,3-dioxopropyl]-4-(benzyloxy)-1-((2*S*,3*R*)-2-
 {[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-
 pyrrolidinecarboxamide

Step (C15a): Following the procedures analogous to steps
 35 (A50) and (B1), the title compound was obtained. MS found
 (M+1)⁺ 950.1.

Example C16

(2*S*,4*R*)-4-(benzyloxy)-*N*-[(1*S*)-3-({2-[(5-[(3-
 40 chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl}amino)-
 2-oxoethyl]amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-

5 ((2S,3R)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide

Step (C16a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found
10 (M+1)⁺ 1046.7.

Example C17

(2S,4R)-4-(benzyloxy)-N-[(1S)-3-({2-[[[1,1'-biphenyl]-3-ylsulfonyl]amino]-2-oxoethyl}amino)-1-(2,2-difluoroethyl)-2,3-dioxopropyl]-1-((2S,3R)-2-{[5-(4-chlorophenyl)-2-furoyl]amino}-3-methylpentanoyl)-2-pyrrolidinecarboxamide
15

Step (C17a): Following the procedures analogous to steps (A50) and (B1), the title compound was obtained. MS found
20 (M+1)⁺ 961.2.

Example D1

N-[(1S,4S,7S)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-[(1R)-1-methylpropyl]-2,5,8,11,12-pentaoxo-3,6,9,13-tetraazahexadec-15-en-1-yl]-2-pyrazinecarboxamide
25

Step (D1a): The α -hydroxyl β -allyl homoallylglycinamide was prepared according to the following reference disclosed in Han, W. et. al, *Bioorg. & Med. Chem Lett.*, 10, 711-713, **2000**, which is hereby incorporated by reference.

30 (D1b): Tripeptide R-Leu-Ile-Cha-OH was prepared following a procedure analogous to Steps (A2a-h).

(D1c): Following a procedure analogous to Step (A1j), the product from (D1a) and (D1b) was coupled to give the desired α -hydroxyamide.

35 (D1d): Following a procedure analogous to Step (A2g), the above α -hydroxyamide was converted to the desired product. MS found (M+1)⁺ 668.3.

5

Example D2

(6*S*, 9*S*, 12*S*)-*N*, 3-diallyl-6-(cyclohexylmethyl)-12-isobutyl-9-
[(1*R*)-1-methylpropyl]-2, 5, 8, 11, 14-pentaoxo-16, 16-diphenyl-
4, 7, 10, 13-tetraazahexadecan-1-amide

10 Step (D2a): Following a procedure analogous to Steps (D1a-
d), the title compound was obtained. MS found (M+1)⁺ 770.9.

Example D3

15 (4*S*, 7*S*, 10*S*)-*N*, 13-diallyl-10-(cyclohexylmethyl)-4-isobutyl-
7-[(1*R*)-1-methylpropyl]-2, 5, 8, 11, 14-pentaoxo-3, 6, 9, 12-
tetraazapentadecan-15-amide

20 Step (D3a): Following a procedure analogous to Steps (D1a-
d), the title compound was obtained. MS found (M+1)⁺ 604.1.

Example D4

N-{(1*S*, 4*S*, 7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-
[(1*R*)-1-methylpropyl]-2, 5, 8, 11, 12-pentaoxo-3, 6, 9, 13-
tetraazahexadec-15-en-1-yl}-2-pyridinecarboxamide

25 Step (D4a): Following a procedure analogous to to Steps
(D1a-d), the title compound was obtained. MS found (M+1)⁺
667.4.

30

Example D5

N-{(1*S*, 4*S*, 7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-
[(1*R*)-1-methylpropyl]-2, 5, 8, 11, 12-pentaoxo-3, 6, 9, 13-
tetraazahexadec-15-en-1-yl}nicotinamide

35 Step (D5a): Following a procedure analogous to to Steps
(D1a-d), the title compound was obtained. MS found (M+1)⁺
667.4.

Example D6

40 *N*-{(1*S*, 4*S*, 7*S*)-10-allyl-7-(cyclohexylmethyl)-1-isobutyl-4-
[(1*R*)-1-methylpropyl]-2, 5, 8, 11, 12-pentaoxo-3, 6, 9, 13-

5

Example D10

((3-[(1-[3-methyl-2-((4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl)amino)pentanoyl]-octahydro-1H-indol-2-yl)carbonyl)amino]-2-oxopentanoyl)amino)acetic acid

10

(D10a): The peptide pyrizinecarbonyl-Leu-Ile-octahydroindazole carboxylic acid was prepared following a procedure analogous to Steps (A2a-h).

(D10b): Following a procedure analogous to Steps (A1j-1), the above peptide was coupled with the product from (A1d) and converted to the desired product. MS found (M+1)+ 672.4.

Example D11

tert-butyl ((3-[(1-[3-methyl-2-((4-methyl-2-[(2-pyrazinylcarbonyl)amino]pentanoyl)amino)-pentanoyl]octahydro-1H-indol-2-yl)carbonyl)amino]-2-oxopentanoyl)amino)acetate

Step (D11a): Following a procedure analogous to Steps (D10a-b), the title compound was obtained. MS found (M+1)+ 728.5.

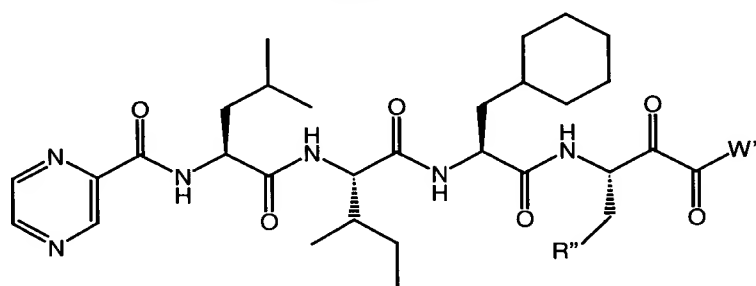
Example D12

(3S,6S,9S,12S)-6-(cyclohexylmethyl)-3-ethyl-12-isobutyl-9-[(1R)-1-methylpropyl]-2,5,8,11,14-pentaoxo-16,16-diphenyl-4,7,10,13-tetraazahexadecan-1-oic acid

(D12a): Tripeptide R-Leu-Ile-Cha-OH was prepared following a procedure analogous to Steps (A2a-h).

(D12b): Following a procedure analogous to Step (A1j), the above tripeptide was coupled to the product from (A1d) to give the desired α -hydroxyester.

((D12c): Following a procedure analogous to Steps (A2e) and (A2g), the above material was converted to the desired product. MS found (M+1)+ 719.6.

Table 1

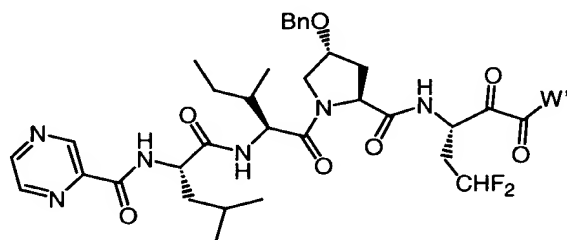
Ex #	R''	W''	(M+1)+
A1	Me	Glycine	674.4
A2	Me	2H-tetrazol-5-yl-methylamino	698.4
A3	Me	Sulfonylmethylamino	710.3
A4	Me	N-[(3-nitrophenyl)sulfonyl]-glycinamide	858.3
A5	Me	N-(methylsulfonyl)glycinamide	751.4
A6	Me	N-[(phenylmethyl)sulfonyl]-glycinamide	825.4
A7	Me	N-(phenylsulfonyl)glycinamide	813.4
A8	Me	N-[(trifluoromethyl)sulfonyl]-glycinamide	805.4
A9	Me	N-[(2-nitrophenyl)sulfonyl]glycinamide	858.1
A10	Me	N-[(4-nitrophenyl)sulfonyl]-glycinamide	858.3
A11	Me	N-[(4-fluorophenyl)sulfonyl]-glycinamide	831.4
A12	Me	N-[(3-fluorophenyl)sulfonyl]-glycinamide	831.4
A13	Me	N-[(2-fluorophenyl)sulfonyl]-glycinamide	831.5
A14	Me	N-[(4-chlorophenyl)sulfonyl]-glycinamide	848.3
A15	Me	N-[(3-chlorophenyl)sulfonyl]-glycinamide	848.4
A16	Me	N-[[4-(thionitroso)phenyl]sulfonyl]glycinamide	870.6
A17	Me	N-[[4-[(trifluoromethyl)sulfonyl]-phenyl]-sulfonyl]glycinamide	946.1
A18	Me	N-[[4-(trifluoromethyl)-phenyl]-sulfonyl]-glycinamide	881.8
A19	Me	N-[(4-cyanophenyl)sulfonyl]-glycinamide	839.0
A20	Me	N-[(3-chloro-4-methylphenyl)-sulfonyl]-glycinamide	862.3
A21	Me	N-[(4-chloro-3-nitrophenyl)-sulfonyl]-glycinamide	893.4
A22	Me	N-[(3,5-dichlorophenyl)sulfonyl]-glycinamide	882.9
A23	Me	N-[(4-methyl-3-nitrophenyl)sulfonyl]-glycinamide	873.1
A24	Me	N-[[2-chloro-5-(trifluoromethyl)-phenyl]-sulfonyl]glycinamide	916.5
A25	Me	N-[(5-carboxy-2-chlorophenyl)sulfonyl]-glycinamide	892.3
A26	Me	N-[(2,5-dichlorophenyl)-sulfonyl]-glycinamide	879.5
A27	Me	N-[(3,4-difluorophenyl)-sulfonyl]-glycinamide	849.6
A28	Me	N-[(3,5-dichloro-2-hydroxyphenyl)-sulfonyl]-glycinamide	895.5
A29	Me	N-[(2,4,5-trichlorophenyl)sulfonyl]glycinamide	913.3
A30	Me	N-[(5-carboxy-4-chloro-2-fluorophenyl)-sulfonyl]glycinamide	(M-1)- 910.6
A31	Me	N-[[5-(dimethylamino)-1-naphthalenyl]-sulfonyl]-glycinamide	907.3
A32	Me	N-(2-naphthalenylsulfonyl)-glycinamide	864.2
A33	Me	N-[(4-(phenyl)phenyl)sulfonyl]glycinamide	889.5
A34	Me	N-[(6-ethoxy-2-benzothiazolyl)-sulfonyl]-glycinamide	915.2

A35	Me	N-[[2-chloro-5-[[(phenylmethyl)-amino]-carbonyl]phenyl]-sulfonyl]glycinamide	980.6
A36	Me	N-[[2-chloro-5-[[(2-trifluoroethyl)-amino]carbonyl]-phenyl]-sulfonyl]glycinamide	970.5 (M-1)-
A37	Me	N-[[2-chloro-5-[[(cyclopropylmethyl)amino]-carbonyl]phenyl]sulfonyl]glycinamide	944.4
A38	Me	N-[[3-nitro-4-(2-pyrimidinylthio)-phenyl]sulfonyl]glycinamide	968.4
A39	Me	N-[[2-chloro-4-(acetylamino)-phenyl]sulfonyl]glycinamide	902.5 (M-1)-
A40	Me	N-[[3-chloro-4-(2-benzoxazolylthio)phenyl]-sulfonyl]glycinamide	1005.5 (M-1)-
A41	Me	N-[[3,5-dichloro-4-(4-nitrophenoxy)phenyl]-sulfonyl]glycinamide	1018.5
A42	Me	N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]-sulfonyl]-glycinamide	878.5
A43	Me	N-[(3-cyanophenyl)-sulfonyl]-glycinamide	838.4
A44	Me	N-[[3-(aminosulfonyl)-5-chlorophenyl]-sulfonyl]glycinamide	924.4 (M-1)-
A45	Me	N-[[3,5-bis(trifluoromethyl)-phenyl]-sulfonyl]glycinamide	949.4
A46	Me	N-{4-[5-(3-(4-chlorophenyl)-3-oxo-1-propenyl)2-furanyl]-phenyl}sulfonyl glycinamide	1043.5
A47	Me	3{[benzylamino]carbonylphenyl-sulfonyl}- glycinamide	946.6
A48	Me	N-[[[[(2-trifluoroethyl)-amino]-carbonyl]phenyl]sulfonyl]-glycinamide	938.5
A49	Me	N-[[3-[(benzylamino)-sulfonyl]-5-chlorophenyl]-sulfonyl]glycinamide	1030.6
A50	CHF ₂	glycine	710.4
A51	CHF ₂	2H-tetrazol-5-yl-methylamino	734.4
A52	CHF ₂	N-[(3,5-dichlorophenyl)-sulfonyl]-glycinamide	918.9
A53	CHF ₂	N-[(3-chlorophenyl)-sulfonyl]-glycinamide	883.3
A54	CHF ₂	N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide	914.5
A55	CHF ₂	N-[3-aminosulfonyl-5-chlorophenyl]sulfonyl- glycinamide	962.4
A56	CF ₃	2H-tetrazol-5-yl-methylamino	752.9
A57	CHF ₂	N-[[[(3-chloro-5-[[(3,3,3-trifluoropropanoyl)amino]sulfonyl]phenyl)sulfonyl]glycinamide	1073.4
A58	CHF ₂	N-[[[(3-chloro-5-[(hexanoylamino)sulfonyl]phenyl)sulfonyl]]glycinamide	1061.3
A59	Me	N-[[[1,1'-biphenyl]-3-ylsulfonyl] glycinamide	890.4
A60	Me	N-[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl] glycinamide	920.1
A61	Me	N-[(3',5'-dichloro[1,1'-biphenyl]-4-yl)sulfonyl] glycinamide	958.5
A62	CHF ₂	N-[(4'-chloro[1,1'-biphenyl]-3-yl)sulfonyl] glycinamide	960.6
A63	CHF ₂	N-{4-(2-methylphenoxy)phenyl}sulfonyl} glycinamide	956.2
A64	CHF ₂	N-[[3-(2-chlorophenoxy)phenyl]sulfonyl] glycinamide	976.3
A65	CHF ₂	OH	653.5
A66	CHF ₂	N-[(4'-methyl[1,1'-biphenyl]-3-yl)sulfonyl] glycinamide	940.1
A67	CHF ₂	N-[[[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-3-yl]sulfonyl] glycinamide	1061.8
A68	CHF ₂	N-[[5-[(4-cyanobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl] glycinamide	1001.9

A69	CHF ₂	N-({5-[(2-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1011.2
A70	CHF ₂	N-({5-[(4-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1006.8
A71	CHF ₂	N-({5-[(3-methoxybenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1007.1
A72	CHF ₂	N-({5-[(3,5-dimethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1004.8
A73	CHF ₂	N-[(3-phenoxyphenyl)sulfonyl] glycinamide	941.8
A74	Me	OH	617.4
A75	CHF ₂	N-({5-[(3-methylbutanoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	957.0
A76	CHF ₂	N-({5-[(hexanoylamino)-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	971.0
A77	CHF ₂	methyloxy glycine	724.4
A78	Me	N-[(3-chloro-5-[(3-chlorobenzoyl)amino]sulfonyl} glycinamide	1066.1
A79	CHF ₂	N-([4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl)sulfonyl} glycinamide	993.9
A80	CHF ₂	N-([1,1'-biphenyl]-3-ylsulfonyl} glycinamide	926.1
A81	CHF ₂	N-({5-[(4-tert-butylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1033.1
A82	CHF ₂	N-[(3-chloro-5-[(3-methylbutanoyl)amino]sulfonyl} phenyl)sulfonyl} glycinamide	1047.7
A83	CHF ₂	4-(4-methoxyphenyl)-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl-methylamino	907.8
A84	CHF ₂	N-({5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1005.2
A85	CHF ₂	N-({5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1011.5
A86	CHF ₂	N-({5-[(3,5-difluorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1013.1
A87	CHF ₂	N-({5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl} glycinamide	1011.3
A88	Me	allylamino	656.4
A89	Me	propargylamino	654.5
A90	Me	t-butyloxy glycine	730.5
A91	Me	benzylamino	706.4
A92	Me	N-pyrrolidinyl	670.3
A93	Me	1,1,1-trifluoroethylamino	698.2
A94	Me	glycinamide	673.4
A95	Me	L-alanine	688.5
A96	Me	L-aspartic acid	732.4
A97	Me	homoglycine	688.5

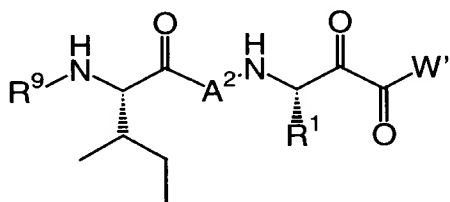
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Table 2



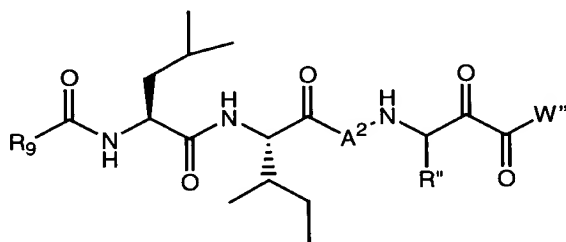
Ex #	W"	(M+1)+
B1	Tert-butyl glycine	816.4
B2	Glycine	760.3
B3	Aminomethyltetrazole	784.4
B4	Methoxyl	717.3
B5	N-[(3-chlorophenyl)-sulfonyl]-glycinamide	933.3
B6	N-[(5-carboxy-2-chlorophenyl)-sulfonyl]glycinamide	978.2
B7	N-[[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl]-glycinamide	982.5 (M+1+H ₂ O)+
B8	N-[(3,5-dichlorophenyl)-sulfonyl]-glycinamide	967.6
B9	N-[(4-methyl-3-nitrophenyl)-sulfonyl]glycinamide	958.4
B10	N-[(3-carboxyl-4-chloro-2-fluorophenyl)sulfonyl]-glycinamide	995.4
B11	N-[[3-chloro-4-(acetylamino)-phenyl]sulfonyl]glycinamide	1116.5
B12	N-[(3-[(benzoylamino)sulfonyl]-5-chlorophenyl)sulfonyl] glycinamide	1117.4
B13	Glycine t-Butylester	788.9
B14	N-[(3-chloro-4-methylphenyl)sulfonyl] glycinamide	948.3
B15	N-[(5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl)sulfonyl] glycinamide	1061.3
B16	Glycine methylester	774.6
B17	N-[(2,4-dichloro-5-methylphenyl)sulfonyl] glycinamide	982.6
B18	N-[(3,4-difluorophenyl)sulfonyl] glycinamide	935.7
B19	N-[(3,4-dichlorophenyl)sulfonyl] glycinamide	1026.7
B20	N-[[4-(3,5-dimethyl-1-piperidiny1)-3-nitrophenyl]sulfonyl] glycinamide	1056.0
B21	N-[(3-nitrophenyl)sulfonyl] glycinamide	944.8
B22	N-[[5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl] glycinamide	1021.1
B23	N-[(2,4-dichloro-5-carboxylphenyl)sulfonyl] glycinamide	1012.6

Table 3



Ex#	R ⁹	A ²	R ¹	W"	(M+1) ⁺
C1	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	glycine	659.4

C2	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(trifluoromethyl-sulfonyl)-glycinamide	790.3
C3	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(3,5-dichlorophenyl-sulfonyl)-glycinamide	866.6
C4	4-chlorophenyl-2-furanylcarbonyl	Cha	Et	N-(3-nitrophenyl-sulfonyl)glycinamide	841.3
C5	4-chlorophenyl-2-furanylcarbonyl	HyPOBn	CH ₂ CHF ₂	aminomethyl tetrazole	769.3
C6	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	2H-tetrazol-5-yl-methylamino-	771.5
C7	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	Gly(OtBu)	803.4
C8	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	Glycine	747.3
C9	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	N-([5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	951.2
C10	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	N-([5-(hexanoylamino)-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	1007.9
C11	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	N-([5-[(4-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	1048.3
C12	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	N-([2-([5-[(4-ethylbenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	1041.8
C13	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	Gly(OtBu)	801.9
C14	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	Glycine	746.0
C15	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	N-([5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	950.1
C16	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	N-([5-[(3-chlorobenzoyl)amino]-1,3,4-thiadiazol-2-yl]sulfonyl)glycinamide	1046.7
C17	[(9-oxo-9H-fluoren-1-yl)carbonyl	HyPOBn	CH ₂ CHF ₂	N-([1,1'-biphenyl]-3-ylsulfonyl)glycinamide	961.2

Table 4

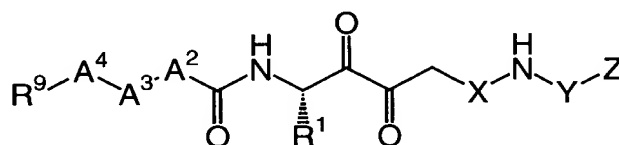
EX#	R ⁹	A ²	R''	W''	(M+1)+
D1	Pyrazine carbonyl	Cha	allyl	allylamino	668.3
D2	3,3-diphenyl propionyl	Cha	allyl	allylamino	770.9
D3	Acetyl	Cha	allyl	allylamino	604.1
D4	2-pyridine carbonyl	Cha	allyl	allylamino	667.4
D5	3-pyridine carbonyl	Cha	allyl	allylamino	667.4
D6	4-nitropyrazole carbonyl	Cha	allyl	allylamino	701.5
D7	2-carboxyl benzoyl	Cha	allyl	allylamino	710.3
D8	3-pyridine carbonyl	Cha	ethyl	allylamino	655.4
D9	3,3-diphenyl propionyl	Cha	ethyl	allylamino	758.8
D10	Pyrazine carbonyl	Octahydro indazole 2-carboxylic acid	ethyl	glycine	672.4
D11	Pyrazine carbonyl	Octahydro indazole 2-carboxylic acid	ethyl	Glycine t-butylester	728.5
D12	3,3-diphenyl propionyl	Cha	ethyl	hydroxyl	719.6

10 The following Table 5 contains representative examples
 envisioned by the present invention. At the start of each
 table is one formula followed by species **Z1** through **Z67**
 demonstrating the intended substitution of Z; species **1a**
 through **1bw** demonstrating the intended substitution of R¹;
 15 and species **9a** through **9n** demonstrating the intended
 substitution of R⁹. Each entry in each table is intended
 to be paired with each formula at the start of the table.
 For example, Example 100 in Table 5 is intended to be
 paired with each of formulae **Z1**, **Z2**, **Z3**, **Z4**, ... through
 20 **Z67** of Table 4, as well as each of formulae **1a**, **1b**, **1c**, **1d**,

5 ... through **1bw** of Table 4, as well as each of formulae **9a**,
9b, **9c**, **9d**, ... through **9n** of Table 4; thereby representing
Example 100-9a-1a-Z1, 100-9a-1a-Z2, 100-9a-1a-Z3, ...
through 243-9n-1bw-Z67.

10 As an illustration, Example 100-9a-1a-Z1 is N-(2-
pyrazinylcarbonyl)-L-leucyl-L-isoleucyl-3-cyclohexylalanyl-
2-oxo-3-aminopentanoyl-N-(methylsulfonyl) glycineamide.

Table 5



Z is selected from:

Z1: methyl	Z21: ethyl
Z2: propyl	Z22: trifluoromethyl
Z3: phenyl	Z23: benzyl
Z4: 4-phenyl-phenyl	Z24: 4-NCS-phenyl
Z5: 2-fluorophenyl-	Z25: 3-fluorophenyl-
Z6: 4-fluorophenyl-	Z26: 2-chlorophenyl-
Z7: 3-chlorophenyl-	Z27: 4-chlorophenyl-
Z8: 2-cyanophenyl-	Z28: 3-cyanophenyl-
Z9: 4-cyanophenyl-	Z29: 2-nitrophenyl-
Z10: 3-nitrophenyl-	Z30: 4-nitrophenyl-
Z11: 2-CF ₃ SO ₂ -phenyl-	Z31: 3-CF ₃ SO ₂ -phenyl-
Z12: 4-CF ₃ SO ₂ -phenyl-	Z32: 2-CF ₃ -phenyl-
Z13: 3-CF ₃ -phenyl-	Z33: 4-CF ₃ -phenyl-
Z14: 3-NO ₂ -4-Cl-phenyl-	Z34: 3-Cl-4-CH ₃ -phenyl-
Z15: 2-Cl-5-CF ₃ -phenyl-	Z35: 2-Cl-5-CO ₂ H-phenyl-
Z16: 3-NO ₂ -4-CH ₃ -phenyl-	Z36: 3-Cl-5-NH ₂ SO ₂ -phenyl-
Z17: 3,5-diCF ₃ -phenyl-	Z37: 3,4-diCF ₃ -phenyl-
Z18: 3,5-diCl-phenyl-	Z38: 2,5-diCl-phenyl-
Z19: 3,4-diCl-phenyl-	Z39: 3,5-diF-phenyl-
Z20: 2,5-diF-phenyl-	Z40: 3,4-diF-phenyl-
Z41: 2-F-4-Cl-5-CO ₂ H-phenyl-	
Z42: 2,4-diCl-5-CO ₂ H-phenyl-	
Z43: 2,4-diCl-5-CH ₃ CO ₂ -phenyl-	
Z44: 2,4-diCl-5-CH ₃ -phenyl-	
Z45: 2-OH-3,5-diCl-phenyl-	
Z46: 2,4,5-triCl-phenyl-	
Z47: 3,5-diCl-4-(4-NO ₂ phenyl)phenyl-	
Z48: 2-Cl-5-benzyl-NHCO-phenyl-	
Z49: 2-Cl-5-CF ₃ CH ₂ -NHCO-phenyl-	
Z50: 2-Cl-5-cyclopropylmethyl-NHCO-phenyl-	
Z51: 2-Cl-4-CH ₃ CONH-phenyl-	
Z52: 5-CH ₃ CONH-1H-pyrrol-2-yl-	
Z53: 5-phenylCONH-furan-2-yl-	
Z54: 2-CH ₃ CONH-2,3-dihydrofuran-5-yl-	

Z55: 3-Cl-5-(phenylCONHSO₂)-phenyl-
Z56: 3-Cl-5-CH₃CONH-phenyl-
Z57: 5-ethoxy-benzothiazol-2-yl
Z58: naphth-2-yl
Z59: (CH₃CONH)thiadiazolyl-
Z60: (s-butyl-CONH)-thiadiazolyl-
Z61: (n-pentyl-CONH)thiadiazolyl-
Z62: (phenyl-CONH)-thiadiazolyl-
Z63: (3-Cl-phenyl-CONH)thiadiazolyl-
Z64: (benzoxazol-2-yl)-
Z65: (1H-benzimidazol-2-yl)-
Z66: thiazolo[4,5-c]pyrid-2-yl-
Z67: 9H-purin-8-yl

5

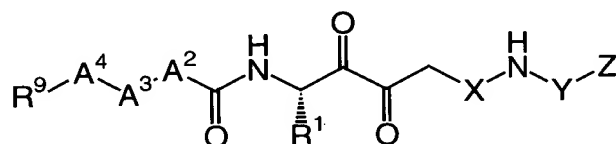
R¹ is selected from:

1a: -CH ₂ CH ₃	1ah: -CH ₂ CH ₂ CH ₂ C(CH ₃) ₃
1b: -CH ₂ CH ₂ CH ₃	1ai: -CH ₂ CH ₂ CH ₂ CH(CH ₃) ₂
1c: -CH(CH ₃) ₂	1aj: -CH ₂ CH ₂ CH ₂ CH(CH ₂ CH ₃) ₂
1d: -CH ₂ CH ₂ CH ₂ CH ₃	1ak: -CH ₂ CH ₂ CH ₂ CH ₂ CH ₃
1e: -CH ₂ CH(CH ₃) ₂	1al: -CH ₂ CH ₂ CH(CH ₃) ₂
1f: -CH ₂ C(CH ₃) ₃	1am: -CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃
1g: -CH ₂ CH ₂ C(CH ₃) ₃	1an: -CH ₂ CHF ₂
1h: -CH ₂ CF ₃	1ao: -CH ₂ CH ₂ CHF ₂
1i: -CH ₂ CH ₂ CF ₃	1ap: -CH ₂ CH ₂ CH ₂ CHF ₂
1j: -CH ₂ CH ₂ CH ₂ CF ₃	1aq: -CH=CH ₂
1k: -CH ₂ CH=CH ₂	1ar: -CH=CHCH ₃
1l: cis-CH ₂ CH=CH(CH ₃)	1as: trans-CH ₂ CH=CH(CH ₃)
1m: -CH ₂ CH ₂ CH=CH	1at: -CH ₂ CH=C(CH ₃) ₂
1n: -CH ₂ CH ₂ CH=C(CH ₃) ₂	1au: phenyl
1o: benzyl	1av: phenethyl
1p: phenpropyl	1aw: phenbutyl
1q: -CH ₂ CO ₂ H	1ax: -CH ₂ CH ₂ CO ₂ H
1r: -CH ₂ CO ₂ C(CH ₃) ₃	1ay: -CH ₂ CH ₂ CO ₂ C(CH ₃) ₃
1s: -CH ₂ CH ₂ CH ₂ CH ₂ NH ₂	1az: (naphth-2-yl)ethyl-
1t: (cyclobutyl)methyl-	1ba: (cyclobutyl)ethyl-
1u: (cyclobutyl)propyl-	1bb: cyclopropyl
1v: cyclobutyl	1bc: cyclopentyl
1w: cyclohexyl	1bd: (4-ethylphenyl)ethyl-
1x: (2-methylphenyl)ethyl-	1be: (4-i-propylphenyl)ethyl-
1y: (3-methylphenyl)ethyl-	1bf: (4-t-butylphenyl)ethyl-
1z: (4-methylphenyl)ethyl-	1bg: (4-hydroxyphenyl)ethyl-
1aa: (2-fluorophenyl)ethyl-	1bh: (2-chlorophenyl)ethyl-
1ab: (3-fluorophenyl)ethyl-	1bi: (3-chlorophenyl)ethyl-
1ac: (4-fluorophenyl)ethyl-	1bj: (4-chlorophenyl)ethyl-
1ad: (2-bromophenyl)ethyl-	1bk: (3-bromophenyl)ethyl-
1ae: (4-bromophenyl)ethyl-	1bm: (4-phenoxy-phenyl)ethyl-
1af: (4-phenyl-phenyl)ethyl-	1bn: (2,5-dimethylphenyl)ethyl-
1ag: (2,4-dimethylphenyl)ethyl-	1bo: (2,6-difluorophenyl)ethyl-
1bp: (4-cyclohexyl-phenyl)ethyl-	
1bq: (4-cyclopentyl-phenyl)ethyl-	
1br: (4-cyclobutyl-phenyl)ethyl-	
1bs: (4-cyclopropyl-phenyl)ethyl-	
1bt: (2-trifluoromethylphenyl)ethyl-	
1bu: (3-trifluoromethylphenyl)ethyl-	
1bv: (4-trifluoromethylphenyl)ethyl-	
1bw: (2,3,4,5,6-pentafluorophenyl)ethyl-	

5 R⁹ is selected from:

- 9a:** 2-pyrazinyl-CO-
9b: 4-(N-pyrrolyl)phenyl-CO-
9c: 5-(4-Cl-phenyl)furan-2-yl-CO-
9d: 1-anthracenyl-CO-
9e: 7-NO₂-anthracen-1-yl-CO-
9f: (3-phenyl-2-cyanomethoxyphenyl)-CO-
9g: 5-(2-Cl-3-CF₃-phenyl)-furan-2-yl-CO-
9h: 5-(4-Cl-phenyl)-furan-2-yl-CO-
9i: 5-(pyrid-2-yl)-thiophen-2-yl-CO-
9j: (2-CH₃O-phenyl)ethyl-CO-
9k: (3-benzopyrrolyl)ethyl-CO-
9l: (N-phenyl-5-propyl-imidazol-4-yl)-CO-
9m: 1-naphthyl-SO₂-
9n: 5-(isoxazol-2-yl)-thiophen-2-yl-SO₂-

Table 5 (cont.)



Ex#	R ⁹	A ⁴	A ³	A ²	R ¹	X	Y	Z
100	9a - 9n	Ile	Leu	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
101	9a - 9n	Val	Leu	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
102	9a - 9n	Dpa	Leu	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
103	9a - 9n	Ile	Val	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
104	9a - 9n	Val	Val	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
105	9a - 9n	Dpa	Val	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
106	9a - 9n	Ile	Glu	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
107	9a - 9n	Val	Glu	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
108	9a - 9n	Dpa	Glu	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
109	9a - 9n	Ile	Leu	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
110	9a - 9n	Val	Leu	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
111	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
112	9a - 9n	Ile	Val	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
113	9a - 9n	Val	Val	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
114	9a - 9n	Dpa	Val	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
115	9a - 9n	Ile	Glu	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
116	9a - 9n	Val	Glu	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
117	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
118	9a - 9n	Ile	Leu	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
119	9a - 9n	Val	Leu	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
120	9a - 9n	Dpa	Leu	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
121	9a - 9n	Ile	Val	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
122	9a - 9n	Val	Val	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
123	9a - 9n	Dpa	Val	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
124	9a - 9n	Ile	Glu	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
125	9a - 9n	Val	Glu	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
126	9a - 9n	Dpa	Glu	Pro	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
127	9a - 9n	bond	Leu	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
128	9a - 9n	bond	Val	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67
129	9a - 9n	bond	Glu	Cha	1a - 1bw	-(C=O)-	-SO ₂ -	Z1 - Z67

130	9a - 9n	bond	Leu	Hyp	1a - 1bw	-(C=O) -	-SO ₂ -	Z1 - Z67
131	9a - 9n	bond	Val	Hyp	1a - 1bw	-(C=O) -	-SO ₂ -	Z1 - Z67
132	9a - 9n	bond	Glu	Hyp	1a - 1bw	-(C=O) -	-SO ₂ -	Z1 - Z67
133	9a - 9n	bond	Leu	Pro	1a - 1bw	-(C=O) -	-SO ₂ -	Z1 - Z67
134	9a - 9n	bond	Val	Pro	1a - 1bw	-(C=O) -	-SO ₂ -	Z1 - Z67
135	9a - 9n	bond	Glu	Pro	1a - 1bw	-(C=O) -	-SO ₂ -	Z1 - Z67
136	9a - 9n	Ile	Leu	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
137	9a - 9n	Val	Leu	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
138	9a - 9n	Dpa	Leu	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
139	9a - 9n	Ile	Val	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
140	9a - 9n	Val	Val	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
141	9a - 9n	Dpa	Val	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
142	9a - 9n	Ile	Glu	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
143	9a - 9n	Val	Glu	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
144	9a - 9n	Dpa	Glu	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
145	9a - 9n	Ile	Leu	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
146	9a - 9n	Val	Leu	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
147	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
148	9a - 9n	Ile	Val	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
149	9a - 9n	Val	Val	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
150	9a - 9n	Dpa	Val	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
151	9a - 9n	Ile	Glu	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
152	9a - 9n	Val	Glu	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
153	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
154	9a - 9n	Ile	Leu	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
155	9a - 9n	Val	Leu	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
156	9a - 9n	Dpa	Leu	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
157	9a - 9n	Ile	Val	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
158	9a - 9n	Val	Val	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
159	9a - 9n	Dpa	Val	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
160	9a - 9n	Ile	Glu	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
161	9a - 9n	Val	Glu	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
162	9a - 9n	Dpa	Glu	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
163	9a - 9n	bond	Leu	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
164	9a - 9n	bond	Val	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
165	9a - 9n	bond	Glu	Cha	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
166	9a - 9n	bond	Leu	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
167	9a - 9n	bond	Val	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
168	9a - 9n	bond	Glu	Hyp	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
169	9a - 9n	bond	Leu	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
170	9a - 9n	bond	Val	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
171	9a - 9n	bond	Glu	Pro	1a - 1bw	-SO ₂ -	-(C=O) -	Z1 - Z67
172	9a - 9n	Ile	Leu	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
173	9a - 9n	Val	Leu	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
174	9a - 9n	Dpa	Leu	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
175	9a - 9n	Ile	Val	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
176	9a - 9n	Val	Val	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
177	9a - 9n	Dpa	Val	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
178	9a - 9n	Ile	Glu	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
179	9a - 9n	Val	Glu	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
180	9a - 9n	Dpa	Glu	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
181	9a - 9n	Ile	Leu	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
182	9a - 9n	Val	Leu	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
183	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
184	9a - 9n	Ile	Val	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
185	9a - 9n	Val	Val	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
186	9a - 9n	Dpa	Val	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
187	9a - 9n	Ile	Glu	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
188	9a - 9n	Val	Glu	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67

189	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
190	9a - 9n	Ile	Leu	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
191	9a - 9n	Val	Leu	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
192	9a - 9n	Dpa	Leu	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
193	9a - 9n	Ile	Val	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
194	9a - 9n	Val	Val	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
195	9a - 9n	Dpa	Val	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
196	9a - 9n	Ile	Glu	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
197	9a - 9n	Val	Glu	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
198	9a - 9n	Dpa	Glu	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
199	9a - 9n	bond	Leu	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
200	9a - 9n	bond	Val	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
201	9a - 9n	bond	Glu	Cha	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
202	9a - 9n	bond	Leu	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
203	9a - 9n	bond	Val	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
204	9a - 9n	bond	Glu	Hyp	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
205	9a - 9n	bond	Leu	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
206	9a - 9n	bond	Val	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
207	9a - 9n	bond	Glu	Pro	1a - 1bw	-(C=O) -	-(C=O) -	Z1 - Z67
208	9a - 9n	Ile	Leu	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
209	9a - 9n	Val	Leu	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
210	9a - 9n	Dpa	Leu	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
211	9a - 9n	Ile	Val	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
212	9a - 9n	Val	Val	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
213	9a - 9n	Dpa	Val	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
214	9a - 9n	Ile	Glu	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
215	9a - 9n	Val	Glu	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
216	9a - 9n	Dpa	Glu	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
217	9a - 9n	Ile	Leu	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
218	9a - 9n	Val	Leu	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
219	9a - 9n	Dpa	Leu	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
220	9a - 9n	Ile	Val	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
221	9a - 9n	Val	Val	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
222	9a - 9n	Dpa	Val	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
223	9a - 9n	Ile	Glu	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
224	9a - 9n	Val	Glu	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
225	9a - 9n	Dpa	Glu	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
226	9a - 9n	Ile	Leu	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
227	9a - 9n	Val	Leu	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
228	9a - 9n	Dpa	Leu	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
229	9a - 9n	Ile	Val	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
230	9a - 9n	Val	Val	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
231	9a - 9n	Dpa	Val	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
232	9a - 9n	Ile	Glu	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
233	9a - 9n	Val	Glu	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
234	9a - 9n	Dpa	Glu	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
235	9a - 9n	bond	Leu	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
236	9a - 9n	bond	Val	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
237	9a - 9n	bond	Glu	Cha	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
238	9a - 9n	bond	Leu	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
239	9a - 9n	bond	Val	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
240	9a - 9n	bond	Glu	Hyp	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
241	9a - 9n	bond	Leu	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
242	9a - 9n	bond	Val	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67
243	9a - 9n	bond	Glu	Pro	1a - 1bw	-SO ₂ -	-SO ₂ -	Z1 - Z67

Chazas 5

UTILITY

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The compounds of Formula (I) are expected to inhibit the activity of Hepatitis C Virus NS3 protease. The NS3 protease inhibition is demonstrated using assays for NS3 protease activity, for example, using the assay described below for assaying inhibitors of NS3 protease. The compounds of Formula (I) are expected to show activity against NS3 protease in cells, as demonstrated by the cellular assay described below. Thus, the compounds of Formula (I) are potentially useful in the cure and prevention of HCV infections.

Expression and Purification of NS3 Protease

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The plasmid cf1SODp600, containing the complete coding region of HCV NS3 protease, genotype 1a, was obtained from ATCC (database accession: DNA Seq. Acc. M62321, originally deposited by Chiron Corporation). PCR primers were designed that allow amplification of the DNA fragment encoding the NS3 protease catalytic domain (amino acids 1 to 192) as well as its two N-terminal fusions, a 5 amino acid leader sequence MGAQH (serving as a expression tag) and a 15 amino acid His tag MRGSHHHHHMGAQH. The NS3 protease constructs were cloned in the bacterial expression vector under the control of the T7 promoter and transformed in *E. coli* BL 21 (DE3) cells. Expression of the NS3 protease was obtained by addition of 1 mM IPTG and cells were growing for additional 3h at 25°C. The NS3 protease constructs have several fold difference in expression level, but exhibit the same level of solubility and enzyme specific activity. A typical 10 L fermentation yielded approximately 200 g of wet cell paste. The cell paste was stored at -80°C. The NS3 protease was purified based on published procedures (Steinkuhler C. et al. *Journal of Virology* 70, 6694-6700, 1996 and Steinkuhler C. et al. *Journal of Biological Chemistry* 271, 6367-6373, 1996.) with some modifications. Briefly, the cells were resuspended in lysis buffer (10 mL/g) containing PBS buffer (20 mM sodium phosphate, pH 7.4, 140 mM NaCl), 50%

5 ~~glycerol, 10 mM DTT, 2% CHAPS and 1mM PMSE. Cell lysis was~~
performed with use of microfluidizer. After homogenizing,
DNase was added to a final concentration 70 U/mL and cell
lysate was incubated at 4°C for 20 min. After
centrifugation at 18,000 rpm for 30 min at 4°C supernatant
10 was applied on SP Sepharose column (Pharmacia), previously
equilibrated at a flow rate 3 mL/min in buffer A (PBS
buffer, 10% glycerol, 3 mM DTT). The column was extensively
washed with buffer A and the protease was eluted by
applying 25 column volumes of a linear 0.14 - 1.0 M NaCl
15 gradient. NS3 containing fractions were pooled and
concentrated on an Amicon stirred ultrafiltration cell
using a YM-10 membrane. The enzyme was further purified on
26/60 Superdex 75 column (Pharmacia), equilibrated in
buffer A. The sample was loaded at a flow rate 1 mL/min,
20 the column was then washed with a buffer A at a flow rate 2
mL/min. Finally, the NS3 protease containing fractions were
applied on Mono S 10/10 column (Pharmacia) equilibrated in
50 mM Tris.HCl buffer, pH 7.5, 10% glycerol and 1 mM DTT
and operating at flow rate 2 mL/min. Enzyme was eluted by
25 applying 20 column volumes of a linear 0.1 - 0.5 M NaCl
gradient. Based on SDS-PAGE analysis as well as HPLC
analysis and active site titration, the purity of the HCV
NS3 1a protease was greater than 95%. The enzyme was stored
at -70°C and diluted just prior to use.

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Enzyme Assays

Concentrations of protease were determined in the absence
of NS4a by using the peptide ester substrate Ac-
DED(Edans)EEAbuψ[COO]ASK(Dabcyl)-NH₂ (Taliani et al. *Anal.*
35 *Biochem.* 240, 60-67, 1996.) and the inhibitor, H-Asp-Glu-
Val-Val-Pro-boroAlg-OH and the inhibitor, H-Asp-Glu-Val-
Val-Pro-boroAlg-OH and by using tight binding reaction
conditions (Bieth, *Methods Enzymol.* 248, 59-85, 1995). Best
data was obtained for an enzyme level of 50 nM.
40 Alternately, protease (63 µg/ml) was allowed to react with
~~3 µM NS4a, 0.10 mM Ac-Glu-Glu-Ala-Cys-pNA, and varying~~

5 ~~level of H-Asp-Glu-Val-Val-Pro-boroAla-OH (0.6 μ M).~~

Concentrations of protease were determined from linear plots of Activity vs. [inhibitor]. Molar concentrations of proteases were determined from the x-intercept.

10 K_m values were determined measuring the rate of hydrolysis of the ester substrate over a range of concentrations from 5.0 to 100 μ M in the presence of 3 μ M KKNS4a (KKGSVVIVGRIVLSGKPAIIPKK). Assay were run at 25°C, by incubating ~1 nM enzyme with NS4a for 5 min in 148 μ l of buffer (50 mM Tris buffer, pH 7.0, 50% glycerol, 2% Chaps, 15 and 5.0 mM DTT. Substrate (2.0 μ l) in buffer was added and the reaction was allowed to proceed for 15 min. Reactions were quenched by adding 3.0 μ L of 10% TFA, and the levels of hydrolysis were determined by HPLC. Aliquots (50 μ L) were injected on the HPLC and linear gradients from 90% 20 water, 10% acetonitrile and 0.10 % TFA to 10% water, 90% acetonitrile and 0.10% TFA were run at a flow rate of 1.0 mL/min over a period of 30 min. HPLCs were run on a HP1090 using a Rainin 4.6 x 250 mm C18 column (cat # 83-201-C) fluorescent detection using 350 and 500 nm as excitation 25 and emission wavelengths, respectively. Levels of hydrolysis were determined by measuring the area of the fluorescent peak at 5.3 min. 100% hydrolysis of a 5.0 μ M sample gave an area of 7.95 ± 0.38 fluorescence units.). Kinetic constants were determined from the iterative fit of 30 the Michaelis equation to the data. Results are consistent with data from Liveweaver Burk fits and data collected for the 12.8 min peak measured at 520 nm.

Enzyme activity was also measured by measuring the increase in fluorescence with time by exciting at 355 nm 35 and measuring emission at 495 nm using a Perkin Elmer LS 50 spectrometer. A substrate level of 5.0 μ M was used for all ~~fluorogenic assays run on the spectrometer.~~

5 Inhibitor Evaluation In vitro

~~Inhibitor effectiveness was determined by measuring~~
enzyme activity both in the presence and absence of
inhibitor. Velocities were fit to the equation for
competitive inhibition for individual reactions of
10 inhibitors with the enzyme using

$$v_i / v_o = [K_m (1 + I/K_i) + S] / [K_m + S].$$

The ratio v_i / v_o is equal to the ratio of the
Michaelis equations for velocities measured in the presence
(v_i) and absence (v_o) of inhibitor. Values of v_i / v_o were
15 measured over a range of inhibitor concentrations with the
aid of an Excel™ Spreadsheet. Reported K_i values are the
average of 3-5 separate determinations. Under the
conditions of this assay, the IC_{50} and K_i s are comparable
measures of inhibitor effectiveness.

20 Using the methodology described above, compounds of
the present invention were found to exhibit K_i 's of $\leq 60 \mu M$,
thereby confirming the utility of the compounds of the
present invention as effective NS3 protease inhibitors.
Preferred compounds of the present invention have K_i 's of
25 $\leq 1 \mu M$. More preferred compounds of the present invention
have K_i 's of $\leq 100 \text{ nM}$. Most preferred compounds of the
present invention have K_i 's of $\leq 10 \text{ nM}$.

Inhibitor Evaluation in Cell Assay.

30 The following method was devised to assess inhibitory
action of test compounds on the HCV NS3 protease in
cultured cells. Because it is not possible to efficiently
infect cells with hepatitis C virus, an assay was developed
based on co-expression in transfected cell lines of two
35 plasmids, one is able to direct synthesis of the NS3
protease and the other to provide a polypeptide analogous
to a part of the HCV non-structural protein containing a
single known peptide sequence highly susceptible to
cleavage by the protease. When installed in cultured cells
40 by one of a variety of standard methods, the substrate
~~plasmid produces a stable polypeptide of approximately~~

5 ~~50KD, but when the plasmid coding for the viral protease is~~
co-expressed, the enzymatic action of the protease
hydrolyzes the substrate at a unique sequence between a
cysteine and a serine pair, yielding products which can be
detected by antibody-based technology, eg, a western blot.
10 Quantitation of the amounts of precursor and products can
be done by scanning film auto-radiograms of the blots or
direct luminescence-based emissions from the blots in a
commercial scanning device. The general organization of the
two plasmids is provided in Scheme 6. The coding sequences
15 for the NS3 protease and the substrate were taken from
genotype 1a of HCV, but other genotypes, eg 2a, may be
substituted with similar results.

The DNA plasmids are introduced into cultured cells
using electroporation, liposomes or other means. Synthesis
20 of the protease and the substrate begin shortly after
introduction and may be detected within a few hours by
immunological means. Therefore, test compounds are added at
desired concentrations to the cells within a few minutes
after introducing the plasmids. The cells are then placed
25 in a standard CO₂ incubator at 37°C, in tissue culture
medium eg Dulbecco-modified MEM containing 10% bovine
serum. After 6-48 hours, the cells are collected by
physically scraping them from plastic dishes in which they
have been growing, centrifuging them and then lysing about
30 10⁶ of the concentrated cells in a minimal volume of
buffered detergent, eg 20 µl of 1% sodium dodecyl sulfate
in 0.10 M Tris-HCl, pH 6.5, containing 1% mercaptaethanol
and 7% glycerol. The samples are then loaded onto a
standard SDS polyacrylamide gel, the polypeptides separated
35 by electrophoresis, and the gel contents then
electroblotted onto nitrocellulose or other suitable paper
support, and the substrate and products detected by
decoration with specific antibodies.

40 Although this invention has been described with
respect to specific embodiments, the details of these
~~embodiments are not to be construed as limitations. Various~~

5 ~~Equivalents, changes and modifications may be made without~~
departing from the spirit and scope of this invention, and
it is understood that such equivalent embodiments are part
of this invention.

10 Preparation of H-Asp-Glu-Val-Val-Pro-boroAlg pinanediol
ester•trifluoroacetate

Preparation of Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-OH.

15 Boc-Val-Pro-OBzl was prepared by dissolving H-Pro-OBzl (20
g, 83 mmol) in 50 mL of chloroform and adding Boc-Val-OH
(18.0 g, 83 mmol), HOBT (23.0g, 165 mmol), NMM (9.0 mL, 83
mmol) and DCC (17.0 g, 83 mmol). The reaction mixture was
stirred overnight at room temperature. The mixture was
20 filtered and solvent was evaporated. Ethyl acetate was
added and insoluble material was removed by filtration.
The filtrate was washed with 0.2N HCl, 5% NaHCO₃, and
saturated aqueous NaCl. It was dried over Na₂SO₄, filtered
and evaporate to give a white solid (30 g, 75 mmol, 90%).
ESI/MS calculated for C₂₂H₃₂N₂O₅ +H: 405.2. Found 405.6.

25 Boc-Val-Val-Pro-OBzl was prepared by dissolving Boc-Val-
Pro-OBzl (14.0 g, 35.0 mmol) in 4N HCl in dioxane (20 mL)
and allowing the reaction to stir for 2h under an inert
atmosphere at room temperature. The reaction mixture was
30 concentrated by evaporation in vacuo and ether was added to
yield a precipitate. It was collected by filtration under
nitrogen. After drying in vacuo with P₂O₅, H-Val-Pro-OBzl
was obtained as a white solid (22.6 g, 30.3 mmol, 89%).
(ESI/MS calculated for C₁₇H₂₄N₂O₃ +H: 305.2. Found:

35 305.2.) H-Val-Pro-OBzl (9.2 g, 27 mmol) was dissolved in
50 mL of CH₂Cl₂ and Boc-Val-OH (7.3 g, 27 mmol), HOBT (7.3
g, 54 mmol), NMM (3.0 mL, 27 mmol) and DCC (5.6 g, 27 mmol)
were added. The reaction mixture stirred overnight at room
temperature. The mixture was filtered and the filtrate was
40 evaporated. The residue was dissolved in ethyl acetate and
~~the solution was re-filtered. The filtrate was washed with~~

5 ~~0.2N HCl, 5% NaHCO₃, and saturated aqueous NaCl. It was~~
dried over Na₂SO₄, filtered and evaporated to give a yellow
oil (10.6 g, 21.1 mmol, 78%). ESI/MS calculated for
C₂₇H₄₁N₃O₆ + Na: 526.3 Found: 526.4.

10 Z-Glu(O^tBu)-Val-Val-Pro-OBzl was also prepared by DCC
coupling. H-Val-Val-Pro-OBzl hydrochloride was obtained in
a 100% yield by treating the corresponding Boc compound
with anhydrous HCl using the procedure described for H-Val-
Pro-OBzl (ESI/MS calculated for C₂₂H₃₃N₃O₄ + H: 404.2.

15 Found 404.3.). The amine hydrochloride (7.40 g, 16.8 mmol)
was dissolved in 185 mL DMF and 25 mL THF. Z-Glu(O^tBu)-OH
(5.60 g, 16.8 mmol), HOBt (4.60 g, 33.6 mmol), NMM (1.85
mL, 16.8 mmol) and DCC (3.5 g, 16.8 mmol) were added. The
20 reaction was run and the product was isolated by the
procedure described for Boc-Val-Val-Pro-OBzl. The
tetrapeptide was obtained as a white foam (12.0 g, 16.1
mmol, 96%). ESI/MS calculated for C₃₉H₅₄N₄O₉ + Na: 745.4.
Found: 745.4.

25 H-Glu(O^tBu)-Val-Val-Pro-OH was prepared by dissolving Z-
Glu(O^tBu)-Val-Val-Pro-OBzl (2.90 g, 3.89 mmol) in 100 mL
methanol containing 1% acetic acid. Pearlman's catalyst,
Pd(OH)₂, (100mg) was added and the flask was placed on the
Parr hydrogenation apparatus with an initial H₂ pressure of
30 34 psi. After three hours, the catalyst was removed by
filtration through a celite pad and the filtrate was
evaporated in vacuo to yield a yellow oil (1.30 g, 2.61
mmol, 67%). ESI/MS calculated for C₂₄H₄₂N₄O₇ + H: 499.3
Found: 499.4.

35 Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-OH was prepared by
active ester coupling. Boc-Asp(O^tBu)-N-hydroxysuccinimide
ester was prepared by coupling Boc-Asp(O^tBu)-OH (3.00 g,
10.4 mmol) to N-hydroxysuccinimide (1.19 g, 10.4 mmol) in
40 50 mL of ethylene glycol dimethyl ether. The reaction
flask was placed in an ice bath at 0°C and DCC was added.

5 ~~The reaction mixture was slowly allowed to warm to room~~
temperature and to stir overnight. The mixture was
filtered and the filtrate was evaporated in vacuo. The
residue was dissolved in ethyl acetate and re-filtered.
The filtrate was evaporated give a white solid.

10 Recrystallized from ethyl acetate: hexane gave the
activated ester (3.38 g, 8.80 mmol, 84%). (ESI/MS
calculated for $C_{17}H_{26}N_2O_8 + H$: 387.2. Found: 387.4.) H-
Glu(O^tBu)-Val-Val-Pro-OH (5.40 g, 10.8 mmol) was dissolved
in 100 mL of water. Sodium bicarbonate (0.92 g, 11.0 mmol)
15 was added followed by triethylamine (2.30 mL, 16.5 mmol).
The N-hydroxysuccinimide ester (3.84 g, 10.0 mmol) was
dissolved in 100 mL dioxane and was added to the H-
Glu(O^tBu)-Val-Val-Pro-OH solution. The mixture stirred
overnight at room temperature. Dioxane was removed in
20 vacuo and 1.0 M HCl was added to give pH ~ 1. The product
was extracted into ethyl acetate. The ethyl acetate
solution was washed with 0.2 N HCl, dried over sodium
sulfate, filtered, and evaporated to yield a yellow oil
(7.7 g, 10.0 mmol, 100%). ESI/MS calculated for $C_{37}H_{63}N_5O_{12}$
25 + Na: 792.4. Found: 792.4.

Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-boroAlg-pinandediol was
prepared by coupling the protected pentapeptide to H-
boroAlg-pinandediol. Boc-Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-OH
30 (1.8 g, 2.3 mmol) was dissolved 10 mL THF and was cooled to
-20°C. Isobutyl chloroformate (0.30 mL, 2.3 mmol) and NMM
(0.25 mL, 2.3 mmol) were added. After 5 minutes, this
mixture was added to H-boroAlg-pinandediol (0.67 g, 2.3
mmol) dissolved in THF (8 mL) at -20°C. Cold THF (~5 mL)
35 was used to aid in the transfer. Triethylamine (0.32 mL,
2.3 mmol) was added and the reaction mixture was allowed to
come to room temperature and to stir overnight. The
mixture was filtered and solvent was removed by
evaporation. The residue was dissolved in ethyl acetate,
40 washed with 0.2 N HCl, 5% $NaHCO_3$, and saturated NaCl. The
~~organic phase was dried with Na_2SO_4 , filtered, and~~

5 ~~evaporated to yield a yellow oil. Half of the crude~~
product (1.5 g) was purified in 250 mg lots by HPLC using a
4 cm x 30 cm Rainin C-18 reverse phase column. A gradient
from 60: 40 acetonitrile: water to 100% acetonitrile was
run over a period of 28 minutes at a flow rate of 40
10 mL/min. The fractions containing the desired product were
pooled and lyophilized to yield a white solid (46 mg). ¹H-
NMR (CD₃OD) δ 0.9-1.0 (m, 15H), 1.28 (s, 3H), 1.3 (s, 3H),
1.44 (3s, 27H), 1.6-2.8 (20H), 3.7(m, 1H), 3.9(m, 1H), 4.1-
4.7 (7H), 5.05(m, 2H), 5.9(m, 1H). High res (ESI/MS)
15 calculated for C₅₁H₈₆N₆O₁₃B₁ +H: 1001.635. Found 1001.633.

Preparation of H-Asp-Glu-Val-Val-Pro-boroAlg pinanediol
ester•trifluoroacetate: The hexapeptide analog, Boc-
Asp(O^tBu)-Glu(O^tBu)-Val-Val-Pro-boroAlg-pinanediol, (22.5
20 mg, 0.023 mmol) was treated with 2 mL of TFA: CH₂Cl₂ (1: 1)
for 2 h. The material was concentrated in vacuo and
purified by HPLC using C-18 Vydac reverse phase (2.2 x 25
cm) column with a gradient starting at 60:40
acetonitrile/water with 0.1%TFA going to 95:5 over 25
25 minutes with a flow rate of 8 mL/min. The product eluted
at 80% acetonitrile. The fractions were evaporated and
dried under high vacuum to give 8.9 mg (49%) of the desired
product as white amorphous solid. ¹H-NMR (CD₃OD) δ 5.82
(m, 1H), 5.02 (m, 2H), 4.58(m, 1H), 4.42 (m, 3H), 4.18 (m,
30 4H), 3.90 (m, 1H), 3.62 (m, 1H), 3.01 (dd, 1H), 2.78 (m,
1H), 2.62 (m, 1H), 2.41-1.78 (m, 17H), 1.31 (s, 3H), 1.28
(s, 3H), 1.10 - 0.82 (m, 15H). ESI/MS calculated for
~~C₃₈H₆₂N₆O₁₁B +H: 789.2. Found: 789.2.~~